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A NEW THEORY OF ALLERGIC PHENOMENA

Mechanism of Hypersensitization, Immune Responses and Allergic Phenomena

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THE allergic phenomena are characterized by abnormal responses to physical and chemical stimuli. Abnormal responses are anaphylaxis, hay fever, asthma, inflammatory and immediate urticarial types of reactions, itching, vesiculation, spongiosis, et cetera. These and many other abnormal manifestations are known as anaphylactic allergy, serum sickness, atopic allergy, contact allergy, drug allergy, et cetera. These allergic types are differentiated from each other by their peculiarities.

Anaphylactic allergy, serum sickness, and atopic type of allergic reactions as a group are believed to be mediated through blood-borne antibodies known as precipitin and reagin. They may be singly or jointly involved in a given case of hypersensitive state and they also elicit an immediate urticarial type of skin reactions. Atopic allergy is characterized by the predominance of a hereditary tendency which is absent in the anaphylactic and serum sickness type of sensitivities.

Bacterial type of allergy is differentiated from the above three types by: (1) a delayed type of inflammatory skin reaction, (2) absence of blood-borne antibody and experimental animal anaphylaxis, and (3) infection with bacteria as a sensitizing process which is different from the type of allergy induced by protein *per se*.

Contact and drug allergies are caused by simple substances of non-protein nature. In these allergies, neither the presence of an hereditary

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tendency nor the participation of any type of circulating antibody has been demonstrated. In the anaphylactic type of allergy the total amount of antibody is distributed in the tissues and blood stream establishing an equilibrium. Replacement of immune blood by normal blood will cause the migration of tissue antibody into the blood stream, thus establishing a new equilibrium. The blood of patients with bacterial or drug allergy has failed to yield any evidence for the existence of similar antibody under any of these conditions.

THE COMMON DENOMINATOR OF ALLERGIES

Despite this diversity, a further discriminatory analysis of data reveals the fact that hypersensitivity, as a common denominator, underlies all allergic phenomena. With this fact as a base line, one may proceed to the formulation of a concept capable of tracing the genesis of all allergic manifestations to a single process.

PRIMARY BASIC PROCESS IN ALLERGIC PHENOMENA

At this point of our discussion the most obvious question therefore is, how do such abnormal responses originate?

It is too elementary to state that any response in a biologic system involves chemical events of measurable magnitude. Abnormality of the response is merely a qualification to the effect that the living system is experiencing an unusual chemical event. The very nature of a biologic event necessitates the utilization of the elementary rules and logic of chemistry for an understanding. Very often we forget or ignore thinking in simple chemical terms. As a rule, substances of opposing chemical affinities interact yielding a product which differs basically from the original reactants. A reaction between ammonia and hydrogen chloride produces ammonium chloride, which is neither like ammonia nor like hydrogen chloride. A reaction between sodium chloride and silver nitrate precipitates highly insoluble silver chloride, which is neither one nor the other of the original reactants. A protein molecule reacting with mercury yields a product which differs in properties from both parent substances. A foreign substance cannot escape the consequence of reacting with and modifying protein molecules. The cells in animal systems must either destroy this foreign substance or suffer the consequences of one or more metabolic modifications. Similarly, dyes and salts of heavy metals have the property of chemically fixing themselves to the proteins of the skin, thereby inducing sensitization and reactions.

In specific instances, substances such as chloramine-T and halazone,[3] and similarly active well known p-chlorobenzoyl chloride, picryl chloride, et cetera, introduced into animal systems, have produced asthma, rhinitis and immediate whealing skin reactions by direct and transfer tests. In these reactions, the involvement of reagin, anaphylactic type of antibody, and precipitins have been indicated. Since the formation of these anti-

bodies took place in the absence of external foreign proteins, the inescapable conclusion appears to be that these nonprotein foreign agents by chemical combinations have alienated the native proteins to the extent of acquiring antigenicity in the environment of their origin. The most significant aspect of these events is, primarily, therefore, not the antibody synthesis, but the events leading to their synthesis. Such alterations which have rendered the native proteins antigenic would seem to be sufficient also to cause the abnormal reactions associated with hypersensitization. Antibody formation would naturally be secondary to the establishment of a more basic mechanism of hypersensitivity which persists for a much longer period of time than any period of antibody formation. Furthermore, the question with which we must be concerned most is the degree of hypersensitivity or alteration in proteins and the amounts of abnormal reaction products with which hosts' metabolic streams may be polluted and impaired. Viewed from this angle, also, antibody, reagin, and the like must be considered as abnormal or potentially toxic products resulting from the actions of foreign agents on host metabolic systems.

HYPERSENSITIZATION AT A MOLECULAR OR PROTEIN LEVEL

The synthesis of immune globulin in response to a species of protein molecule shows clearly that gamma globulin can undergo as many modifications as there are species of protein molecules capable of acting as antigens. These alterations are specific chemical events. The idea that tissue proteins undergo alterations is a logical realism destined to clarify the interactions associated with allergic manifestations. Alterations of tissue proteins by reactions with foreign substances can result from denaturation, liberation of -SH or formation of -S-S- groups, and also from changes in the states of aggregation or polymerization, shape, solubility, modified antigenicity, biologic activity, and susceptibility to various agents. The persistence of these changes from generation to generation of cells would suggest that the continued synthesis of altered proteins in these cells must be mediated by altered self-duplicating hypersensitive systems.

An alteration in a protein molecule is primarily an injury. Abnormal or allergic manifestations represent therefore a composite or sum of injuries inflicted upon the various proteins in a cell. The examination of the genesis of the mechanism of hypersensitivity at a molecular or protein level assumes a much greater significance if we realize the fact that, as the seats of the determinants of enzymatic and antigenic specificities, proteins dominate and regulate the entire functions of cells and tissues. Furthermore, endowed with potentially active biocatalytic centers and numerous polar or reactive groups such as carboxyl, imidazol, guanidyl, peptide linkages, hydrogen bonding, et cetera, the proteins exist in a dynamic state and are therefore chemically the most vulnerable entities in a cell. Any foreign reactive substance which enters the animal system

and cannot be disposed of immediately is destined to alter certain cell proteins and thereby establish hypersensitive mechanisms.

It is also a condition of this point of view to regard the allergic phenomenon as simply another manifestation of a potentially active general process in all living systems. Behaviors such as dependence of cells on growth factors following mutations, tolerance to toxic agents, tolerance and addiction to narcotics, action of carcinogenic agents in causing tumor growth, auto-immunization arising from the exercise of antigenicity by abnormally altered native proteins, et cetera, may be looked upon as modifications of lasting nature in the proteins of respective living systems.[17]

ESTABLISHMENT OF A HYPERSENSITIVE MECHANISM AS PREPARATORY TO ANTIBODY SYNTHESIS

It was postulated in the introductory remarks that an acquired hypersensitive mechanism may underlie, as a common denominator, all allergic phenomena. The phenomenon of secondary immune response, which has given occasion to various unsatisfactory speculations, would seem to us to be intimately related to the hypersensitive mechanism. The sequence of events permits the following conclusions. The action of foreign proteins on specific sensitive sites of the host can entail injury and repair, chemical readjustments and finally the formation of an active complex by combining with the host enzyme system for the synthesis of altered globulins or antibody. The appearance of antibody in measurable amounts requires a latent period of about eight to fifteen days. During this period the mechanism of hypersensitivity appears to become established, which outlasts any period of antibody synthesis. The existence of such a hypersensitive mechanism is strongly indicated by the following sequence of events.

SECONDARY RESPONSES TO ANTIGENS ASSOCIATED WITH HYPERSENSITIVITY MECHANISM

Following the cessation of antibody synthesis, a re-exposure to the same antigenic material provokes a secondary response with the resumption of antibody synthesis within three to four days. During the secondary response the amount of antibody produced is often from 100 to 1,000 times greater than the amount produced during the period following the onset of primary antibody synthesis. In other words, antigenic action has established a specific hypersensitive state which persists as a potentially active mechanism. It responds readily to secondary antigenic stimulus and functions more efficiently without necessitating the much longer latent preparatory period of about eight to fifteen days preceding the primary response for antibody synthesis. This ready mechanism of hypersensitivity may afford not only a noteworthy defense against infectious agents when the host is

re-exposed to them, but also would be provoked to action by restimulations by allergic agents. On the other hand, an accelerated inflammatory response adduced from previous contacts to antigen is a common aftermath to infection with many organisms. A hypersensitive state may also facilitate the spread of secondary infections. Furthermore, according to Watson,[21] Group A streptococci, growing within the environment of the host, produce a soluble factor or factors capable of preparing the tissues for subsequent damage by Gram-negative toxin.

As in primary response, also in secondary responses to antigenic and other stimulations, the striking feature is the specificity of the response. One must assume therefore that the affected cell systems must have been specifically hypersensitized. A further strong evidence for the induction of a specific hypersensitive mechanism in cells is their necrosis resulting, for example, from the action of tuberculin. In tissue cultures of macrophages of tuberculous animals, tuberculin added to such a culture kills the hypersensitive cells, in concentrations in which cells from nontuberculous animals are unharmed. Before death, the hypersensitive cells lost motility, became round and vacuolate, the cytoplasm became granular, and necrosis ensued.[13] It must be concluded that the previous actions of tubercular materials have induced in the cells an enduring abnormal or detrimental metabolic pattern which may be inactive normally, but on re-exposure to inducing agents are activated resulting in the death of the hypersensitive cells; only the tuberculin fraction of the tubercle bacillus elicits this reaction.[1a,10a] It would thus appear that one of the important characteristics of macrophages is their ability to undergo structural and abnormal metabolic adaptations characteristic of the hypersensitive state. Paralleling the mechanism of sensitivity to foreign agents, the findings of Lurie[12] demonstrated that the tubercle bacillus multiplied freely in normal rabbits, whereas its growth was much reduced or inhibited in rabbits previously infected with tubercle bacilli. This resistance to reinfection did not depend on the presence of antibody, but instead resulted from an increase of phagocytic activity of monocytes and their capacity to destroy tubercle bacilli. Suter's[19] findings may be interpreted to indicate that monocytes of sensitized animals have experienced changes in the intracellular metabolism whereby the tubercle bacilli failed to grow.

In this connection, the following observation by J. H. Hanks[10] is of interest. He stated that "It was only in those individuals who exhibited a definite, delayed-type, necrotic skin reaction to test proteins that there developed later from 10 to 100 times more antibody than in those who failed to exhibit the phenomenon. I believe, therefore, that Dienes and Malloney were correct in suggesting that tuberculin type sensitization represents a magnification of the usually mild, delayed type sensitivity which precedes antibody production. For some reason which is not yet clear, the response to proteins of the tubercle bacillus appears to remain more persistently in this early phase of immunological response."

INDUCED MORPHOLOGICAL CHANGES ASSOCIATED WITH THE ORIGIN OF HYPERSENSITIVE STATE

Gay and Claypole[4] found that reinjection of immune animals with homologous bacteria produced a hyperleukocytosis; that is, typhoid immune animals receiving typhoid bacilli would respond with a few fold greater number of leukocytes than the normal animals under the same treatment. Gay and Morrison[5] studying the question of resistance to streptococcus infection found similar results. Zinsser and Tsen[21] reported that when Gram-negative bacilli (*B. typhosus, B. coli*) prodigiosus, which may be antigenically related to each other through somatic antigen, are injected into typhoid immunized animals, there was a definitely higher number of leukocytes in the immunized animals than in normal controls similarly treated. In the case of Gram-positive bacteria, in animals immunized with homologous bacteria there was a more marked difference between the immunized and normal animal response. Cannon and Pacheco,[1] studying tissue immunity, reported an early markedly large pouring of mononuclear cells in the areas where the host has had similar experience previous to reinvasion. These observations suggest that a new mechanism has been established during the first invasion, whereby in response to reinvasion the time required for the mobilization of polymorphonuclear cells is brief and the response is more intense. An idea about the origin of this accelerated mechanism may be gained from an examination of the primary responses to antigenic and parasitic stimulations as discussed below.

The inoculation of antigenic and nonantigenic foreign material is shown to be a most potent method of inducing proliferations in the reticuloendothelial (macrophage) system. The cells of this system ingest the antigenic molecule or particles, store vital dyes and are active in inflammation and immunity. Sabin[14] reported that coincident with the time when the antigen, dye-protein, is no longer visible within these cells, and when there are antibodies in the serum, there is a marked acceleration (over that of the normal rate) of the shedding of the surface films of the macrophages without damage to them. Good[6,7] and Good and Varco[8,9] reported that antigenic stimulation induces in the bone marrow vigorous maturation of cells of the hematopoietic reticulum along the plasma cell line. Various induced changes include: (a) increase in the size of lymph nodes; (b) increased numbers and activity of germinal centers; (c) increased proliferation of lymphocytes; (d) proliferation of the cells of the fixed reticulum; (e) cytoplasmic budding of lymphocytes; and (f) significant plasma cell accumulation, especially pronounced in the medullary cords. Morphologic evidence has indicated that the plasma cells may have developed largely from the reticulum and from mesenchymatous elements, also from the very basophilic reticular lymphocytes. Since the development of plasma cells from reticulum is accelerated several fold by the ingested antigenic fragments, it is easily conceivable that antigens are carried over with the plasma cells and therein mediate

antibody synthesis. Fagraeus[2] reported that a beginning differentiation of a reticulum cell into a plasma cell is marked, *inter alia,* by an increase in its cytoplasmic basophilia; the interrelationship between the basophilia of a cell and its content of ribonucleotides appears to be associated with the capacity to form antibodies.

The above enumerated morphologic and chemical changes in response to the action of antigen appear to be associated with alterations in cell physiology adapted to the hypersensitive state. Furthermore, the persistence of hypersensitivity in the absence of antigen or antibody synthesis implicates a self-duplicating mechanism innate either to the reticuloendothelial system or to a pre-existing system from which the reticular cells originate.

DISSOCIATION OF HYPERSENSITIVITY FROM ANTIBODY SYNTHESIS

Good[8] has reported also that in agammaglobulinemia patients, antigenic stimulation produced: (a) gross hypertrophy of the lymph node; (b) some lymphocytic proliferation; (c) a considerable degree of cytoplasmic budding of the lymphocytes; (d) proliferation of the cells of the reticulum; and (e) notable failure of secondary follicle formation characterized the nodes of these patients. These may be regarded as initial tissue changes in response to antigenic stimulation as preparatory to the establishment of the hypersensitive state without involving the operation of immune mechanisms. In these patients no plasma cellular proliferation occurred, indicating that profound malfunction of the reticulum existed. In agammaglobulinemic patients, Janeway, Apt and Gitlin[11] and others observed: (1) absence of gamma globulin in patients' sera; (2) absence of circulating antibody in the blood and tissues; (3) failure of antibody production in response to antigenic stimulation; and (4) increased susceptibility to bacterial infections. Good[7] reported absence of Forssman antibody, complement fixing and virus neutralizing antibodies, commonly found in the serum of normal patients. Finally, isoagglutinins to blood group substances in agammaglobulinemic patients were completely absent. Furthermore, successful homotransplantation of skin in these patients indicated absence of antibody production.

However, as reported by Good[6] and Good and Varco,[8,9] the bacterial type of hypersensitivity occurs in agammaglobulinemic patients in absence of the ability to synthesize normal or immune gamma globulins. Good[7] reported also that, after dermal application of 2,4-dinitrofluorobenzene, four agammaglobulinemic patients developed a delayed type of sensitivity. This could be transferred with cells to a nonsensitive person. Also, each of the patients reacted positively to skin testing with Schick and Dick toxins, indicating an absence of tissue antibodies against these ubiquitous antigens.

Development of a hypersensitive state in agammaglobulinemic patients, failure of plasmacellular proliferation, and failure to gain impetus from

antigenic stimulation to induce in the bone marrow maturation of cells of the hematopoietic reticulum along the plasma cell line, would seem to show that immune antibody does not play a role in any of the hypersensitive states established in agammaglobulinemic patients.

COMPETITIVE ANATAGONISM IN IMMUNE REACTIONS

At this point I wish to introduce the concept of competitive antagonism in immune reactions and possibly also in allergic and hyposensitization reactions. The competition is between antibody and metabolites or similar substances for the reactive sites in antigenic or allergenic molecules. A toxin, for example, produces its effect by reacting with something in the host. This *something* is the substrate for toxin, since in catalytic amounts it produces its action. The toxin cannot exercise an action on its specific substrate unless they are attracted mutually. Similarly, the antigen and antibody are mutually attracted. Thus, an antigen, or pollen, or toxin, must exercise its affinities in the direction of two competing antagonists. This is the basis for the competitive antagonism between the substrate and antibody for a union with toxin, or enzyme-antigen, or pollen. This immune competitive antagonism cannot be observed in test tube experiments limited to neutralization or precipitin reactions. Conditions *in vivo* are different, which must be taken into consideration in hyposensitization attempts and prophylactic measures. Neutralization of a factor in test tubes is no guarantee that the behavior of that factor *in vivo* will be the same.

We will consider at this point the hyposensitization attempts in atopic conditions in the light of competitive antagonism. It is known that hyposensitization is difficult, requires numerous injections over a long period, is only quantitatively moderate, and that tolerance thus produced is lost quickly. There does not seem to be a direct proportionality between the amount of reagin in serum, clinical manifestations, and positive skin test. This discrepancy is attributed to the neutralization of pollen or its extract by a thermostable blocking antibody leaving reagin free. This is believed to result from a competition between two antibodies, the blocking antibody and reagin for a single reactive group in pollen. However, unlike standard antibody reactions, the reaction of blocking antibody with pollen fails to produce injurious side reactions. Why the blocking antibody and pollen combination does not produce histamine or the like in a manner comparable to antigen-antibody reactions is difficult to understand. In this connection, one may perhaps be permitted to inquire about the possibility of pollens acting as toxins or biocatalysts on hypersensitive sites and producing allergic manifestations in a manner qualitatively comparable to the toxic action of tuberculin on hypersensitive macrophages. On this basis, one may suggest the idea that the blocking antibody may exercise the important role of neutralizing the toxic actions of pollens.

THE BASIS OF IMMUNE COMPETITIVE ANTAGONISM

Enzyme-antienzyme, toxin-antitoxin reactions have demonstrated beyond doubt the need for re-evaluation of immunologic data to account for the competition between a metabolite and antibody for union with biologically active antigen.[15,16,18] The question we must answer is: "By what specific mechanism does a foreign protein introduce a combining-specific modification into a globulin molecule during its synthesis?" We believe that an antigen can accomplish this fact only if it can act as a highly specialized biocatalyst.[15,16] Biocatalysts are the only known entities which are capable of endowing with structural specificity molecules the synthesis of which they mediate. The synthesis of *dextro* and *levo* rotatory natural compounds, sugars with *alpha* or *beta* configuration, scores of type-specific pneumococcal polysaccharides, et cetera, are mediated by enzymes with biocatalytic specificity centers. We believe that any foreign protein in combination with the host synthetic enzyme system exercises a directed biocatalytic role in specifically modifying the synthesis of immune globulin. Experimental data gathered from immunologic studies show that the part an antigen plays in the synthesis of immune globulin satisfies fully the well-known criteria of catalysis. The sole function of an antibody, as far as it is known, is to block an antigen's biologic activity. This function of antibody is subject to competitive antagonism by specific substrates or metabolites. The high order of the specificity manifested in this competition can only serve to bring out the basic fact that the mediation of the antibody synthesis and the metabolism of substrates must be directed by the same specificity center in the antigen-biocatalyst. It may seem paradoxical, but it is a fact that the same catalytic centers in a protein molecule are responsible for the alien antagonistic function, namely, production of an antibody in a foreign host which suppresses the native and physiologically critical function of the same protein molecule. This paradox originates from the fact that the specificity of the enzyme-substrate reaction and that of the enzyme-antienzyme reaction constitute a unity within a given catalytic center of a protein. This unity of antagonistic specificities must be reckoned in immunologic reactions involving antigens, pollens, plant materials, toxins, enzymes, et cetera. Failure or success in attempts of hyposensitizations may depend upon whether or not the system involves immune competitive reactions.

DRUG TOLERANCE AND ALLERGIC PHENOMENA

As discussed above, the synthesis of antibody is a well-known example of alterations which the host proteins are capable of sustaining. The alterations are governed by the determinant centers of specificity of the inciting foreign proteins. This specificity is also induced into the hypersensitive tissue proteins. On the other hand, nonprotein substances, such as aspirin, quinine, lipids, resorcinol, heavy metals, gold, bismuth, arsenic,

chromium, et cetera, lack specificity determinant centers. However, they bring about general chemical modifications in tissue proteins and produce nonspecific or similar allergic reactions.

While the anaphylactic type of allergy can be explained by a reaction between tissue antibody and specific antigen, such an explanation cannot account for the reactions in allergies in which antibody has not been shown to form or to exist. It would seem reasonable to conclude therefore that the allergic reactions must be mediated by a mechanism involving alterations in the tissue proteins themselves. Different reactions observed in different patients might therefore be looked upon as different aspects of the same basic reaction occurring on a molecular or protein level.

Experimental data gathered from different disciplines, such as tolerance to drugs manifested by microorganisms, abnormal growth, tolerance and addiction to narcotics, mutation, et cetera, as discussed elsewhere,[17] seem to show that these phenomena also involve alterations in the proteins of the respective systems. It would seem therefore that these manifestations which appear unrelated might be different phases of a single process occurring in different disciplines at the protein level. Since in all these systems, metabolic functions, growth, regeneration and reproduction are mediated by enzymes, the focus of our critical study must be the enzyme proteins as subject to alterations resulting in metabolic disorders, allergic manifestations and other abnormalities.

HYPERSENSITIVITY TO ANTIMICROBIAL DRUGS

Of the antimicrobial drugs, sulfonamides and penicillin have been shown to cause hypersensitivity more than the other antibiotics. A fuller account can be obtained from results with sulfonamides.

The discussion of our subject is perhaps sufficiently advanced to attempt a synthesis using various findings from related fields. This synthesis must utilize the information gathered from studies on the action of sulfonamides on microbial enzymes, the biochemical modifications which microbes undergo on acquiring tolerance, the action of sulfonamides on tissue enzymes, and the possible changes they may undergo on acquiring hypersensitivity to this drug.

Action of Sulfonamides on Microbial and Tissue Enzymes.—Sulfonamides exercise their antibacterial action by combining chemically with microbial enzymes. Sulfonamides have been shown also to inhibit the numerous animal tissue enzymes. One may therefore suggest that sulfonamides can bring about their allergic effects by interfering with tissue enzymes.

The toxicology of the sulfonamides is well known to every practicing physician. Standard books on pharmacology devote considerable space to the subject which we need not go into here. What interests us here most are the abnormal manifestations of allergic nature caused by sulfonamides.

Renal hypersensitivity, recurring drug fever apparently resulting from sensitization to drug, incidence of dermatitis, skin eruptions of every morphologic type appearing between the eighth and the twelfth day following the administration of the drug, and the persistence of sensitization for several years are manifestations which no doubt are related to the action of the drug on tissue enzymes.

Mechanism of Hypersensitivity to Sulfonamides.—It is evident from clinical observations that after an incubation period of eight to twelve days a patient may acquire a lasting hypersensitivity to sulfonamides. Following this period, the burst of allergic eruptions indicates that the toxic effects of the drug on the enzyme systems reached its climax with the show of pathologic reactions. This is indicative of an established state of hypersensitivity since it may respond severely on re-exposure to the drug several years later. The predominance of allergic metabolism by replacing the normal type at the site of unhealthy tissue indicates that an abnormal metabolic pattern specific for and induced by the drug has been established. In the absence of drug it may revert to normal, entirely or in part, and recurs when re-exposed to the drug. A comparable alteration happens also in the metabolism of a microbe which has acquired tolerance to a drug.

On this basis, hypersensitivity to a drug is a phenomenon of tolerance and not intolerance. You may question me on this point. The basic mechanism of hypersensitivity is a phenomenon comparable to drug tolerance in microbes. As in bacteria, the latent period preceding allergic manifestations is a period of lasting metabolic readjustments under the action of drug. As in sensitive bacterial cells, sensitizing agents gradually build up a lasting modification in the protoplasm. From the standpoint of death or survival the acquistition of the allergic process by cells may be looked upon as means of acquiring a degree of tolerance and thereby escaping total destruction. Bacteria acquire this drug tolerance at the expense of certain metabolic processes and abnormal metabolism in certain others in the presence of drugs. Nature has endowed living cells with innate elemental wisdom of parting under duress with certain metabolic patterns or accepting substitute patterns or alterations in enzyme activities to escape total destruction. These capabilities may be biologic prerequisites for the self-preservation of the species. Let me state at this point that, compared with the parent drug sensitive cell, a sulfonamide resistant daughter strain is a sick strain. It is as sickly, as the person who is allergic to sulfonamides. We have several drug-resistant bacteria which have lost several synthetic abilities, and even are dependent on drugs for growth. We do not know any bacteria which have acquired tolerance without suffering enduring incompetence.

As cited before, tuberculin exercises a killing action on tuberculin hypersensitive monocytes in tissue culture. Tuberculin has significantly

less action on monocytes from nontuberculous animals. It therefore shows that a tuberculin specific metabolic pattern has been established in the hypersensitive monocytes. This pattern apparently is relatively inactive under normal conditions and operates when in contact with the specific inducer. Similarly, bacteria which have acquired tolerance to a drug manifest, in contact with the drug, similar abnormal specific metabolic behavior which is different from the metabolism exercised in the absence of drug. In addition, as discussed above, the drug-tolerant cell has also distinctly altered metabolic patterns which differentiate it from the parent sensitive cells. No method has been found as yet to restore the metabolism of the original drug-sensitive cell to drug-tolerant offspring. In the therapy of allergy the aim of course is not to kill the hypersensitive cells but to restore them to healthy condition. It is a question whether any of the present practices have systematically succeeded in achieving this objective.

CONCLUSION

Ever since the evolution of the first model from amino acids, the protein molecule has been undergoing various structural modifications giving rise to myriads of distinct living entities. This has been realized because of the possibility with which the union of amino acids with each other can take place to produce countless numbers of specifically active patterns. Furthermore, the presence of numerous reactive polar groups enable the protein molecule to undergo many modifications within itself. This is exemplified by the capacity of the gamma globulin molecule to acquire in the form of immune bodies as many specific modifications as there are antigenic proteins. Also, since enzyme-proteins in cells are labile, exist in a dynamic state, and are constantly in action, of all the cellular components, they are most vulnerable to the action of foreign agents with simple chemical structure. It seems fairly certain that these agents can influence cellular proteins *per se*, producing characteristic changes of enduring nature and, perhaps, thereby inducing the emergence of hypersensitive mechanisms in the cells. This is an aspect of a basic process which appears to occur in all living cells. The action of toxic agents on microbes producing tolerant strains with reduced and altered metabolism; action of radiation on cells producing a variety of mutants with genetic blocks associated with loss and alteration of metabolism; action of carcinogenic substances on mammalian cells causing the genesis of tumors; action of narcotics on animal system producing abnormal physiologic behavior and addiction, may tentatively be considered as different manifestations of a basic process occurring in different living systems. The phenomenon of allergy appears to us as another manifestation of similar nature accompanied with abnormal metabolic activities with and without contact of the inducer.

It would seem that a capacity for undergoing enduring alterations under

adverse conditions is a biologic prerequisite for the maintenance and perpetuation of the living form under changing conditions. Tissue cells acted upon by foreign agents are induced, in some subtle manner, to part with certain normal activities and accept less favorable alterations as a way out for survival. The acquisition in this manner of an hypersensitive mechanism may therefore be looked upon as an adaptive process to escape destruction. Microbes, plants, protozoa, lower and higher animals are endowed with this escape mechanism.

The reduction of the complex mass of allergic data to simple bases may permit the flow of vast amounts of useful knowledge from other related disciplines to the study of allergy. It may also permit an opportunity for a re-evaluation of data and reorientation of our views from the standpoint of effective therapy.

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SCHERING AWARD-WINNING STUDENTS ANNOUNCED

The prize winners in Schering Corporation's 1955 international medical writing contest have recently been announced. The successful contestants were Charles King Mervine and David Charles Schechter, both of whom attend Jefferson Medical College in Philadelphia, who co-authored the two prize-winning papers, topping entries from more than eighty other medical schools. The subjects of their papers were "The Prevention and Treatment of Blood Transfusion Reactions" and "The Management of Osteoporosis." This is the first time in the history of the Award that two students from the same school have taken first prizes for reports in two of the three given medical subjects. The third top prize on the subject, "Recent Trends in the Clinical Use of Adrenocortical Steroids" was written jointly by Frank A. Migliorelli of Georgetown Medical School, Washington, D. C., and Salvatore Leone of the State University of New York College of Medicine at Brooklyn. The second prize winners on each subject have also been announced.

The Eleventh Annual Schering Award Competition is now under way, on the subjects: "The Clinical Use of Adrenocortical Steroids in Collagen Diseases"; "Metabolic Aspects of the Aging Process"; and "New Applications of Antihistamines in Medicine and Surgery."

PHYSIOLOGIC AND PATHOLOGIC ALLERGY

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TO BE the guest speaker at the luncheon meeting of The American College of Allergists is certainly a great honor, which you can be sure I highly appreciate, just as I feel proud to be an honorary member of your society. However, on the one hand, I feel somewhat strange to talk about allergy to allergists, but on the other hand I am pleased to think back over the years and discuss with you my experiences and thoughts on the subject since the time I was so closely associated with Pirquet and his fundamental study of this problem.

About fifty years ago, the term allergy was coined by Pirquet, at which time he and I evolved a theory which is still valid. Progress has, of course, been made in details of clinical observation and in the treatment involved in your specialty of allergy, but it must be borne in mind that this specialty is only a part of the larger problem involved in the comprehensive term, "allergy."

Your specialty has tremendous practical importance, as it deals with a peculiar and widespread ailment from which human beings suffer. Consequently, it seems that we are prone to forget the mechanisms involved in the much more extensive part of allergy, which often result in just the opposite of suffering—which constitute one of nature's greatest gifts to mankind.

The symptoms accompanying an allergic asthmatic attack are most imposing and spectacular when resulting in an anaphylactic shock, and are capable not only of killing guinea pigs but can also prove fatal to human beings. This unfortunate side of allergy causes us, at times, to overlook the fact that allergy is really our savior, for which we should ever be thankful to nature, since without allergy we could not survive.

During November, 1955, I attended a very interesting and well organized symposium on tuberculosis. Many outstanding experts took part. During the meeting the use of tuberculin as a measure of immunity was discussed. In this connection the question was raised whether allergy has anything at all to do with immunity. The raising of this question surprised me, because Pirquet and I had always pointed out that allergy's most important function is that it is the basis of immunity. Such a question could only be brought up if the basic facts concerning allergy are misunderstood.

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As a guest speaker at the Twelfth Annual Congress of The American College of Allergists, in New York, Professor Schick presented the above address under the auspices of the Pediatric Allergy Session, Dr. Howard G. Rapaport, Chairman, April 20, 1956.

If one doubts and destroys the thesis that allergy is the basis of immunity, then Pirquet's allergy collapses like a house of cards.

Such a misunderstanding deserves to be corrected. It is most likely due to the fact that Pirquet's fundamental observations were made in his work on serum sickness. The study of the incubation time gave us the clue to the understanding of allergy. The usual explanation of the incubation period in exotoxic diseases like diphtheria is that it is the time required to produce a sufficient amount of primary toxin (exotoxin) to develop symptoms of the disease. It is of interest to note that the incubation period of this disease is relatively short and not fixed.

Another group of diseases, such as smallpox, smallpox vaccination, measles, and typhoid fever, has a relatively fixed incubation period of eight to fourteen days. This is so constant that we can tell in advance when an infected individual will show the first manifestations of the disease.

In view of these observations, we assumed that the symptoms of such a disease are due to the effect of "endotoxic" substances present and enclosed within the body of the germ, which are set free by "bacteriolytic" and "bacteriocidal" antibodies. Therefore, the explanation of the incubation period in these conditions is that the production of the antibodies requires from eight to fourteen days.

These two explanations are not applicable to the incubation period existing in serum sickness, which follows an injection of horse serum or other animal serum into the human organism. Here the incubation period is also about eight to twelve days and is relatively fixed, being independent of the amount of serum injected. Serum as such is not toxic. It is a dead substance and does not multiply. There is no "endotoxin" to be set free.

Pirquet observed that when a child was reinjected with horse serum several weeks after the first injection, it showed immediate symptoms following the reinjection. There was no incubation period. Hence, it was called an "immediate reaction."

In further studies Pirquet and Schick showed that when a child was reinjected with horse serum four months or more after the first injection, there was no immediate, but an accelerated, reaction; i.e., the child developed symptoms of serum sickness within four to six days—a decidedly shorter incubation period compared with the reaction after the first injection. It was realized that such reactions—immediate and accelerated—have diagnostic value. When an individual treated with horse serum gives an immediate or an accelerated reaction, a diagnosis of a previous injection of serum may be made even without any actual knowledge of such an injection. This fact gave Pirquet the idea that skin tests may be applied for the diagnosis of a previous contact with the pathogenic substance or of a previous invasion by a germ or virus. Pirquet may, therefore, be regarded as the father of all skin testing for diagnostic purposes.

Skin tests which have the most significant clinical application are the tuberculosis test and those employed in asthma, hay fever, urticaria, eczema, and many other skin rashes. Pirquet realized that the horse serum itself could not be responsible for the difference in incubation time, because the reinjected serum may have been taken from the same bottle as the initially injected serum. He concluded, therefore, that there must have been some change in the child to explain the difference in incubation time. The reactivity of the child must have been altered. For this altered reactivity of the individual a new term was needed, and in 1906 Pirquet coined the word "allergy."

In order to explain allergy, or altered reactivity, we formulated the following theory. Horse serum is a foreign protein, which, when introduced subcutaneously or intravenously (parenterally), acts as a foreign body and is not tolerated in our system. It must be destroyed. The destruction is carried out by antibodies, which act in a manner similar to digestive ferments in the destruction of protein in the gastrointestinal tract. Every day we consume different foreign proteins which are broken down in the gastrointestinal tract to amino acids. Intermediary toxic products appear which are rapidly passed and detoxified, partly within the intestinal wall and partly, after absorption, in the liver, so that no toxic symptoms ensue. The situation is different when a foreign protein is injected parenterally. In that case, antibodies are formed.

In the interaction between the antigen (foreign protein) and the antibodies, intermediary toxic products are also formed which are not detoxified and are responsible for the clinical symptoms. These antibodies, once produced, stay within the circulation. Therefore, should the same kind of protein be reinjected, it comes immediately in contact with its antibody, and so an immediate reaction follows. After four to six months, the antibodies gradually disappear. Nevertheless, they can be reproduced more rapidly in case of reinjection and, therefore, an accelerated antigen-antibody interaction takes place. Both forms of reaction, the immediate and accelerated, have diagnostic value.

No immunity exists in serum sickness. In this disease the existence of allergy has only diagnostic value. In this case, allergy is unpleasant, unwanted, and even dangerous. The allergic reaction is not only an immediate or accelerated one, but is frequently more intensive and even leads, at times, to collapse and death. Hypersensitiveness was known to Koch, Behring, and Theobald Smith. Richet studied Actiniavenom and found a peculiar kind of hypersensitiveness for which he coined the term "anaphylaxie."

From these observations we perceive that the statement that "allergy does not lead to immunity" is correct when relating to allergy in serum sickness and in all diseases of a similar nature. This means that there is no immunity for asthma, hay fever, pollen asthma, urticaria, eczema, and food allergies. In other words, there is no immunity in all the condi-

tions belonging to the empire of the allergists of today. This constitutes a pathologic form of allergy.

Treatment is successful if the offending substance can be avoided. Symptoms can be mitigated by adrenalin and other antiallergic drugs, particularly antihistamines. Hyposensitiveness can be produced by repeated injections with the offending substance. But real immunity has not been accomplished. Nature, otherwise acting so beneficially, in this respect causes unexpected, harmful, and even deadly results. Should it be concluded that the whole allergic mechanism of nature is a mistake? This is not likely.

When Pirquet observed the change in the duration of the incubation time, he realized the importance of this biologic phenomenon for general medicine. Pirquet and I did not disregard the unpleasant, pathologic symptoms accompanying the altered reactivity. But these pathologic symptoms were much less significant than the fundamental implications of allergy upon the understanding of nature's mechanism of defense against our great enemies, bacteria and viruses. These are foreign substances which must either be prevented from invading the organism, or, if they have succeeded in entering, must be eliminated with as little damage as possible.

Therefore, Pirquet turned his attention to the infectious diseases, especially to smallpox vaccination. This disease belongs to the so-called endotoxic diseases. The incubation time is a relatively fixed one. Time is needed for the mobilization of antibodies which are bacterio- or virolytic or bacterio- or virocidal. These antibodies will set free a toxic substance inside the virus or germ. It was at first necessary to study whether immediate and accelerated reactions exist in this disease as they do in serum disease. Should this be the case, then the mechanism of the reaction would be the same as in serum disease but with a different result. The first attack of the disease has a long incubation time, permitting an undisturbed multiplication of the invading germ. With the appearance of antibodies, the virolytic process stops the multiplication, setting free a rather large amount of the endotoxin. The disease is the result of this action of the antibodies and the payment for our victory over the disease.

Antibodies persist after the disease is over. Any reinfection would find the organism prepared, as its antibodies would be present. They can go into action immediately and kill the invading germ. Under these circumstances the virus or germ has almost no time to multiply. The antibodies can set free only an insignificant amount of endotoxin. The clinical effect of such a small amount of endotoxin is minimal or even invisible. Such an individual is considered immune.

As in serum sickness, after the circulating antibodies have disappeared, a repeated invasion of bacteria or virus can again occur. Also, in infectious diseases the antibodies reappear more rapidly and terminate the multiplication of the germ more swiftly than they did the first time. The

amount of endotoxin set free will be smaller and the disease therefore will be much milder. The shorter the incubation time, the milder will be the disease. Pirquet's classic study of vaccination against smallpox proved the correctness of his statements.

Apparently, nature, in principle, makes use of the same mechanism of defense as in serum sickness, but in smallpox vaccination, as in all endotoxic diseases, it is of great advantage to the individual. And so we see that in endotoxic diseases allergy establishes immunity. This is a physiologic and beneficial form of allergy which is needed for sustaining health.

I have pointed out that the study of allergy led to many tests of diagnostic value. A test can be established only if the substance can produce a wheal reaction or an inflammatory reaction at the site of injection. This is not always the case. Tetanus toxin, for example, does not produce an inflammation. No skin test for tetanus immunity or susceptibility exists. It would be very important and helpful to have a skin test for poliomyelitis susceptibility or immunity. Unfortunately, no skin test as yet exists. The tests used in allergy to protein substances produce, if positive, an urticarial wheal, and not, as a rule, inflammation.

It is now time to discuss briefly the different concepts concerning the pathogenesis of allergic reactions. The theory propounded by Pirquet and Schick, that allergic and hyperergic reactions are due to an interaction between antigen and antibodies, is still valid, and many experimental facts (passive transfer, reversed serum sickness, et cetera) support it.

There are, of course, many other theories concerning the pathogenesis of allergic and anaphylactic (hyperergic) reactions. One of those advocated by certain French investigators (Villaret, Vallery-Radot and others) is to the effect that the symptoms of allergy may depend upon an excess of acetylcholine or upon some disturbance in its normal breakdown by the choline esterase. Urbach contends that acetylcholine and similar substances are formed as the end results and not immediately by the interaction of antigen-antibody.

Doerr is the outstanding champion of the physical theory as the basis of the anaphylactic shock. He assumes that the antigens and antibodies, substances of high molecular weight, react on the cell membrane but do not penetrate it. As a consequence, physico-chemical changes are instituted which act as irritants to the cells. According to Bronfenbrenner, the interaction between antigen and antibody serves to disturb the delicate adjustment of the colloidal conditions existing in the serum as well as at the surface of the tissue cells. Widal looks upon anaphylactic shock as representing a disturbance of the colloidal balance. He and his school designate the changes of the colloids in the blood observed during attacks as "hemoclastic crisis" and those in the tissues as colloidoclasia. Lumiere, on the contrary, explains the nature of anaphylactic phenomena on the basis of invisible flocculation occurring in the blood stream of allergic individuals as the result of the encounter between antigen and serum

antibody. In support of his views he cites the fact that *in vitro* flocculation follows the mixture of the antigen with the serum of allergic individuals.

These various theories may have an important bearing in explaining the anaphylactic shock, but cannot be applied as an explanation for all allergic phenomena.

The important role which, apparently, histamine plays at least in eliciting certain symptoms like sneezing, itching, wheal formation, and urticaria was reason for trying antihistamines for the treatment of these symptoms. There is no doubt that these symptoms can be effectively influenced by Benadryl® and Pyribenzamine.®

The prompt effect of adrenalin upon an asthmatic attack and upon urticarial eruption led to the study of the influence of ACTH and cortisone upon allergic conditions, and this particularly on account of the interference of cortisone preparations upon antigen-antibody reactions. If we are correct in assuming that allergic symptoms are due to antigen-antibody interaction, cortisone should be a very potent endocrine hormone to interfere with such interaction. We do know that eczema and other allergic conditions may improve under the action of cortisone.

It should not be forgotten that the inhibition of an antigen-antibody reaction can be a double-edged sword. Such an inhibition may be at a given moment desirable because it is considered advisable to stop an undesired reaction. On the other hand, it could be disadvantageous or even dangerous to inhibit other antigen-antibody reactions which are beneficial and necessary for our fight against other infecting germs. Therefore, the simultaneous use of antibiotics is advised when cortisone is used. Cortisone treatment should be of limited duration, and the patient should be watched for symptoms of a damaging effect caused by cortisone.

Some facts about the tuberculin reaction are worth mentioning. It is an inflammatory reaction different from the wheal reactions which are elicited by the testing of protein-sensitive patients. The chemical constitution of tuberculin is still not well known. For individuals free from tuberculosis, it is absolutely not toxic even in a large dose. One cc of concentrated old tuberculin is tolerated without any symptoms. It is toxic only for individuals harboring a tuberculous focus. Furthermore, no passive transfer could, until lately, be accomplished. I have now found a recent report (Editorial: Passive transfer of delayed cutaneous reactivity to tuberculin by a special plasma protein fraction. Ann. Allergy, 13:422, July-Aug., 1955) which removes this difficulty in explaining the allergic character of the tuberculin reaction. Excerpts from this report follow:

"Tuberculin contains two biologically active components. One is a polysaccharide which is actively antigenic. It appears to be a fraction of tuberculin which is absorbed upon the surface of erythrocytes and becomes the reagent for the demonstration of circulating antibodies in many cases of tuberculosis.

"This fraction, however, does not evoke the delayed type of response so characteristic for the classical tuberculin reaction. This reaction is produced by another component of tuberculin which is a protein of low molecular weight known to us as PPD (Purified Protein Derivate). Being thus marked as the component against which the allergic reaction of the tuberculous patient is directed, it has been the despair of the immunologists, because of the poor ability to evoke an antibody response which would permit its demonstration by any of the classic methods *in vitro* and *in vivo*."

The reaction using PPD can be demonstrated in tuberculous patients. It has been shown that these antibodies are in all likelihood directed against the tuberculin effect. The protein substance must always be present in very small amounts.

"Col and Favour, working with tuberculin positive guinea pigs, report that they have succeeded in obtaining passive transfer of the delayed type of reactivity against PPD with a subfraction of alpha globulin for the isolation of which they elaborate a new method. This fraction contains also the reactivity with Boyd's reagent. By contrast, the antibody to the polysaccharides is found in the gamma globulin fraction of plasma. It is important to note that the gamma globulin has an inhibitory effect upon the alpha fraction which carries the agent of delayed type reactivity. This may explain several puzzling features of previous investigators."

In conclusion, I wish to state that there are two forms of allergy. One is a physiologic and beneficial form, making it possible to fight against diseases due to the invasion of pathogenic microorganisms and leading to immunity. The other form develops after invasion or injection of foreign protein, which as a foreign substance must be eliminated. This elimination is carried out with a similar mechanism of defense, but the allergy is undesirable, harmful and therefore pathologic. It is accompanied by hypersensitivity which may be even endangering life. This form of allergy does *not* lead to immunity.

Physiologic allergy is life saving and outweighs by far the disadvantageous symptoms seen in cases of pathologic allergy. Anaphylaxis is the most intensive effect of pathologic allergy.

FIRST INTER-AMERICAN CONFERENCE ON OCCUPATIONAL MEDICINE AND TOXICOLOGY

The University of Miami School of Medicine and the University of Havana, Cuba, School of Medicine will jointly sponsor the first Inter-American Conference on Occupational Medicine and Toxicology in Miami, Florida, September 3 to 7, 1956. The conference will be repeated next year in Havana. Spanish will be the official language. Dr. Homer F. Marsh, Dean of the School of Medicine of the University of Miami, will be the general chairman. Speakers on the program will come from Venezuela, Mexico, Peru, Colombia, Chile, Puerto Rico, Cuba and the United States. Some of the subjects to be discussed are work and fatigue in industry, establishment of a medical department in industry, recording of medical case histories, control of malaria in endemic areas, occupation and heart disease, treatment of berylliosis and of manganese intoxications.

A METHOD OF REDUCING REACTIONS IN INTRAVENOUS PYELOGRAPHY WITH AN ANTIHISTAMINE

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and
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IN a four-year study of intravenous pyelography covering more than one thousand cases, an attempt was made to minimize reactions to the dye by the addition of an injectable antihistamine, chlorprophenpyridamine maleate (Chlor-Trimeton® maleate), to the contrast media.

The inherent danger of severe and fatal reactions following injections of drugs or foreign proteins during therapeutic and investigational procedures often is a deterrent to their use.[5,8,12] To eliminate or reduce allergic and untoward reactions has led to persistent and exhaustive searches for adequate measures and techniques.[1,2,4,6,9] This study is an outgrowth of studies begun more than five years ago in an attempt to reduce reactions to injectable drugs.

In an exhibit at The American College of Allergists' meeting in April, 1952, a report of which was later published in the ANNALS OF ALLERGY, one of us (M.D.S.) was able to demonstrate a reduction of reactions in highly sensitive patients by mixing pollen with an antihistamine.[10] When penicillin-sensitive patients were similarly injected, there were no systemic reactions, and several patients who had allergic reactions following urography performed in the usual manner were free of untoward effects following mixtures of the dye and an antihistamine.[7]

There have been many articles written since then about the use of antihistamines given orally and in various intravenous mixtures to reduce or prevent reactions to the intravenous injection of contrast media, with varying degrees of success.

Wechsler[13] mixed 10 mg of diphenhydramine hydrochloride (Benadryl®) with contrast media just before the intravenous injection. He reported on a limited number of reactions—urticaria, nausea, vomiting, feeling of warmth, and shock—and he estimated a reduction of reactions to 1 per cent in the 220 patients so treated.

Simon and his co-workers[11] published a preliminary report on an uncontrolled series of 146 patients who were injected with a mixture of 5 mg of chloroprophenpyridamine maleate, in which the over-all rate of reaction was about 4 per cent.

Winter[14] used mixtures of 10 mg of chlorprophenpyridamine maleate

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and sodium acetrizoate (Urokon®). He reported a significant reduction in urticaria and nausea but no material influence on other nonallergic reactions, which he felt may be related to other factors such as the speed of injection and psychogenic effect.

Bursack and Whitaker[3] injected diphenhydramine hydrochloride (20 mg) intravenously just before giving 30 cc of 35 per cent iodopyracet (Diodrast®). They concluded that the routine use of diphenhydramine hydrochloride is not warranted either for the antiemetic or the antihistaminic properties of the drug. It remains problematic, they stated, whether larger doses of the antihistamine would prevent severe anaphylactoid reactions in allergic persons and whether such doses would be tolerated by the patients. They also concluded that side reactions in the allergic category occurred more frequently in patients with an allergic background. A personal history of severe asthma is a definite contraindication to the use of iodopyracet in their experience.

In this series, asthmatic and allergic individuals were not excluded, in contradistinction to most previous studies in urography. As a matter of fact, all patients who had severe reactions during previous pyelography were specifically included in the study.

PROCEDURE

In this study, 20 to 25 cc of the contrast medium (sodium acetrizoate or sodium iodomethanate) was drawn into a 30 cc syringe, and 1 cc of a specially prepared solution of chlorprophenpyridamine maleate, 20 mg, was added. The solution was then injected rapidly into the basilic or median vein, and the reactions of the patient noted.

The special mixture was given to 623 patients, and 379 controls received the dye alone.

REACTIONS TO SODIUM ACETRIZOATE

When sodium acetrizoate was used as the contrast medium, a sensation of heat and thirst was a common experience, but it was twice as frequent in the control subjects as in those given the special mixture. Cough, nausea, vomiting, and urticaria were much less frequent and of a milder character in patients who had been protected with the antihistamine.

Twelve patients who had histories of severe reactions during several previous pyelographies were given the chlorprophenpyridamine mixture. Eleven of these patients were asymptomatic, and only one had a reaction considerably milder than his previous experience. He was treated symptomatically and was relieved of his symptoms in fifteen minutes. This patient was the only one in the entire series of patients given the special mixture to have even a moderately severe reaction.

REACTIONS TO SODIUM IODOMETHANATE

The reactions with sodium iodomethanate were similar to those reported as occurring with sodium acetrizoate. Those patients who received mix-

TABLE I.

	Urokon			Neo-Iopax		
	Dotter et al	Control	With Chlortrimeton	Dotter et al	Control	With Chlortrimeton
Heat	100%	57%	30%	92	35	20
Weakness	80	16	12	72	15	6
Headache	32	3	5	80	6	3
Nausea	40	33	16	36	20	11
Vomiting	12	10	2	16	5	0.8
Coughing	44	13	5	60	4	2
Thirst	72	16	11	84	30	20
Urticaria	20	3	1	8	2	0.8
Arm Pain	20	10	5	24	20	10
Flush	68	12	9	80	15	8
Pallor	28	1.5	3	44	0.6	0.8
Wheezing	4	1	0.2	4	0	0
Sneezing	4	1	0.2	0	0.6	0
Itching	24	3.5	3	4	3	0
Palpitations	24	4	11	20	6	2

Note: This table compares results in our series with a similar table compiled by Dotter, Wetchler and Steinberg, who recorded reactions in contrast media used in angiocardiography.

tures of media and the antihistamine had about 50 per cent fewer reactions, and where symptoms did occur they were generally milder.

DISCUSSION

The percentage of patients who had had previous urograms was the same in both the experimental and control groups. The percentage of prior reactions was twice as frequent in those receiving the chlorprophenpyridamine mixture. It is therefore significant that not a single anaphylactic reaction occurred in the sensitive group, and that there was a four-fold reduction in reactions.

Those patients with a history of allergy, including twenty-one asthmatic patients (six in the control series), had no appreciable increase in reactions, even of a mild variety. Of particular interest were the following: (1) One patient had four previous intravenous pyelograms with increasing severity of symptoms following each pyelography. When given the mixture of antihistamine and contrast medium, he was asymptomatic. (2) Another patient had five previous intravenous pyelograms, all with serious reactions. When the antihistamine was added to the contrast medium, he was asymptomatic, except for slight nausea. (3) Fourteen other patients with a history of previous severe reactions were free of symptoms when given the special mixture.

Investigators frequently report a limited number of observations or artificially separate them into allergic, toxic, or psychogenic reactions, and their reports correspond with this artificial separation. In our experience we found it very difficult completely to divorce allergic reactions from toxic or drug reactions. We therefore recorded all symptoms and complaints of the patients during and after intravenous injections of the dye with or without the antihistamine. We compared the results in several ways.

Table I compares results in our series with a similar table compiled by

TABLE II.

	No. of Patients	History of:			Reaction Rates		
		Previous I.V.P.	Previous Reaction to I.V.P.	Allergy	Mild	Moderate	Severe
Neo-Iopax	178	30%	9%	6%	27.6%	7%	2%
Urokon	201	46	10	8	45	3	2
Neo-Iopax with chlortrimeton	122	35	25	14	12.2	0	0
Urokon with chlortrimeton	501	46	46	9	19.4	0.2	0

Note: No severe reactions occurred in 623 patients who received the special mixtures.

Dotter, Wetchler, and Steinberg, who recorded reactions in contrast media used in angiocardiography.

To separate psychogenic reactions from allergic or toxic effects was similarly a questionable matter. We therefore charted in this series the history of previous reactions of intravenous pyelographs, the history of patients' allergy as well as the severity of reactions noted in Table II.

RESULTS

1. Allergic reactions (urticaria, asthma, et cetera) were virtually eliminated. No anaphylactic reactions occurred in the series injected with the antihistaminic mixture.

2. Other reactions (local arm pain, burning, tingling, et cetera) were greatly reduced in severity as well as percentage-wise.

3. Patients who had violent reactions on previous pyelographies had little or no trouble using the above technique.

4. The injectable antihistamine alone was used as a therapeutic agent in a few cases where anaphylactic reactions occurred in routine pyelograph, as previously reported by one of us (M.D.S.).

CONCLUSIONS

A variety of untoward reactions both minor and severe is a common experience in urography. Efforts to eliminate or reduce dangerous reactions by the use of screening skin tests, ocular tests, and premedication with oral or injectable antihistamines have been unsuccessful. Previous studies with small doses of antihistamine-contrast media mixtures have shown some reduction in reaction rates. In this present series we used 20 mg of chlorprophenpyridamine maleate in mixtures with contrast media. The most important feature of our study was the elimination of severe shock reactions and the reduction of moderately severe reactions. The over-all reduction in reactions was four-fold.

We therefore concluded that when 20 mg of this antihistamine and contrast media were mixed in the same syringe prior to intravenous injection it produces a significant reduction in reactions in urography. A history of allergy was not found to be a contraindication when this procedure was followed.

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Submitted April 23, 1956

AMERICAN COLLEGE OF PHYSICIANS

More than 4,500 persons attended the thirty-seventh annual session of The American College of Physicians at Los Angeles, California, April 16 to 20, 1956. Dr. Walter L. Palmer of Chicago, Illinois, was inducted as president, and other officers elected were: Dr. Richard A. Kern, Philadelphia, Pennsylvania, president-elect; Dr. Chester M. Jones, Boston, Massachusetts, first vice president; Dr. George H. Anderson, Spokane, Washington, second vice president; Dr. Truman G. Schnabel, Sr., Philadelphia, Pennsylvania, third vice president; Dr. Wallace M. Yater, Washington, D. C., secretary-general; and Dr. William D. Stroud, Philadelphia, Pennsylvanita, treasurer.

The 1957 meeting will be held April 8-12 in Boston, Massachusetts, and the 1958 session is scheduled for Atlantic City, New Jersey, April 28 to May 2.

EFFECT OF INJURY TO, AND ELECTRICAL STIMULATION OF, HYPOTHALAMIC AREAS ON ANAPHYLACTIC AND HISTAMINE SHOCK OF THE GUINEA PIG

A Preliminary Report

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IN 1952, one of us[1,2,3,4] reported that a bilateral focal lesion inflicted to the tuberal region of the hypothalamus by means of a Horsley-Clarke stereotactic apparatus inhibited the development of anaphylactic shock in the guinea pig in the majority of cases. Further investigations revealed that the antishock action involved a blocking of antibody production; at the same time there was reason to believe that there existed another site of action, apparently within the framework of the second, nonspecific phase of anaphylactic shock. Since experimental studies of the antishock action have shown that the hypothalamic lesion had no influence either on the antigen-antibody union, or on the liberation of tissue material, it had to be assumed that the second site of action might be an increase in the resistance to biologically active substances in the tuber-lesioned system.

In order to elucidate this point, experiments with guinea pigs were carried out. By means of a Horsley-Clarke stereotactic apparatus, bilateral focal lesions were inflicted to the tuberal region of the hypothalamus. Seven days after operation, the animal was given 1½ times the lethal dose (7 mg/kg body weight) of histamine, subcutaneously. The results for the total of 179 guinea pigs involved were as follows:

1. Thirty-four per cent of the tuber-lesioned animals developed the symptoms of severe shock, but survived.
2. The survivors were given another dose of histamine (7 mg/kg) six weeks after recovery from shock. This time all succumbed, as did the controls.
3. When histamine poisoning was induced seven weeks after lesioning, no protection was observable.

Thus, the above experiments lent full support to our view that the other site of action in the antishock effect of tuber lesion is to be sought in the second, nonspecific phase of anaphylactic shock. Moreover, the finding that protection was transient only suggested the assumption that it is not so much the electrolytic lesioning, i.e., a functional absence, of the hypothalamic areas in question that is responsible for the antishock action, but rather a stimulation of adjacent nervous structures by the periphery of the lesion (by the zone of the vital tissue reaction demarcating necrosis).

On the basis of these considerations, in subsequent experiments attempts

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have been made to reproduce the assumed excitatory state of functional preponderance in single hypothalamic areas, by means of electrical stimulation with indwelling constant electrodes. These experiments were carried out in the Institute of Physiology, Medical University, Pécs. Using the Horsley-Clarke stereotactic technique, bipolar silver electrodes were inserted into different areas of the guinea pig hypothalamus. After complete recovery from surgical trauma (usually two days after insertion of the electrodes), the animals were stimulated with a generator, supplying quadrangular impulses. The amplitude, duration and frequency of impulses could be changed one by one.

The experimental procedure was as follows: The histamine (as specified above) or the anaphylactic shock were elicited and stimulation was begun right away on giving the injection. The current was then applied (according to a well-defined stimulation scheme) for an average of twenty minutes, at one-minute-intervals. A total of 119 guinea pigs were included in this series.

Sixty per cent of the animals survived the anaphylactic shock, and about 45 per cent survived the histamine shock. Subsequent histologic studies have shown that the maximum protection could be achieved by the electric stimulation of the mammillary region, or of the tuberomamillary junction, and not by stimulating the anterior and medial hypothalamic areas, i.e., the tuberal nuclei.

Experience has shown us that in single cases the above procedure could save animals in the gravest state of toxicosis.

A detailed description of the above two series of experiments will be published in *Acta Medica Hungarica.*

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Submitted March 30, 1956

EDITOR'S NOTE

In recommending publication of this compressed version of the interesting work by the researchers in Professor Gömöri's department, one of the reviewers said: "While the subject is highly experimental and the data given are meager, it is subtitled a preliminary report, presages a fuller report and, altogether, is a well written statement. I believe it will grace an issue of the ANNALS, will remind readers that there are unusual laboratory approaches to problems in allergy, and finally may smooth the path of resumption of international scientific intercourse."

HUNGARIAN ALLERGY SECTION

Prof. K. Hajós of Budapest announces that the Hungarian Allergy Section has again resumed its activities and wishes to re-establish relations with other allergy groups throughout the world.

HIGH BLOOD EOSINOPHILIA IN FOOD ALLERGY

A Case Report

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ALTHOUGH I have observed blood eosinophilia in many patients with food allergy, the following case warrants publication for three reasons: (1) the very high level of eosinophils attained (up to 97 per cent); (2) the rapid elevation of eosinophils after ingestion of the allergen; and (3) the fact that the only symptom was fatigue.

CASE HISTORY

On October 23, 1946, Mrs. R. E. T., aged forty-five, was sent into my office by a small-town physician, who stated over the telephone that the patient's blood count revealed a rather severe anemia and a 40 per cent eosinophilia. On arrival at my office, laboratory studies were made which revealed 2,850,000 red blood cells, 50 per cent hemoglobin (Sahli), and 12,000 white blood cells, of which 97 per cent were mature eosinophils. Several smears were made, some stained by Giemsa and others by Wright. The history, both family and personal, was negative for hay fever, asthma, sinus, eczema, urticaria, et cetera. The only complaint was extreme exhaustion and easy fatigability. A complete physical examination was entirely normal, and stool examination revealed no parasites nor ova but 21 per cent eosinophils.

Skin testing with the major food and inhalant allergens resulted in a 4-plus reaction to milk only. The patient admitted that she normally used much milk and cheese.

She was placed on a milk-free diet, but no other therapeutic measurses were instituted. After two weeks on this regimen she returned without breakfast for laboratory studies. At that time the blood count revealed 3,700,000 red blood cells, hemoglobin 70 per cent, 1,600 white blood cells, 18 per cent eosinophils, 30 per cent lymphocytes, and 52 per cent neutrophils. Two hours later, following ingestion of two glasses of milk, the count remained the same, except that the eosinophils had increased to 32 per cent. A week later the fasting blood counts revealed the same picture. The patient reported that when she avoided milk and milk products she felt well and experienced no exhaustion.

She did not return, and I was unable to get her to do so. However, on January 25, 1955, her sister consulted me because of atopic asthma of two years' duration. Through her we persuaded the patient to return. On March 7, 1955, eight and one-half years after her first examination, laboratory studies showed a fasting blood count of 4,470,000 red blood cells, hemoglobin 90 per cent, 12,900 white blood cells, with 69 per cent neutrophils, 2 per cent stabs, 22 per cent lymphocytes, 6 per cent eosinophils, and 1 per cent basophils. Two hours later, following the ingestion of two glasses of milk, the eosinophil count had risen to 12 per cent but all other findings remained constant.

The patient had been in robust health and had not developed any allergic symptoms, but she had carefully avoided milk products because she experienced exhaustion and malaise if she partook of them.

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Submitted March 26, 1956

Survey on Undergraduate and Graduate Education in Allergy

This section of the May-June issue of the ANNALS OF ALLERGY is devoted to detailed reports of the survey made by the American Foundation for Allergic Diseases on the subject of undergraduate and graduate education in the field of allergy. The reports are self-explanatory.

INTRODUCTION TO SURVEY

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THE survey on "Undergraduate Medical Education in Allergy" was conducted through questionnaires addressed on the one hand to deans of medical schools and on the other to members of Alpha Omega Alpha (honorary medical school fraternity). Included are copies of the questionnaires sent, a statistical analysis of the questionnaire, and analyses of the two sets of questionnaires by Drs. Giles A. Koelsche, Assistant Professor of Medicine (Allergy) at the Mayo Graduate School, Rochester, Minnesota. Dr. Koelsche is also a member of the Scientific and Educational Council of the American Foundation for Allergic Diseases.

The survey on "Graduate Education in Allergy" was conducted through questionnaires sent to all the medical schools in the United States and to certain other institutions in which it was known that some type of graduate instruction in allergy was being conducted. A copy of the questionnaire is included. The replies to the questionnaire were then turned over for evaluation and analysis to Dr. Richard A. Kern, Professor of Medicine at Temple University, Philadelphia, Pennsylvania. Dr. Kern is also a member of the Scientific and Educational Council of the American Foundation for Allergic Diseases. Dr. Kern's analysis and evaluation are published herewith in full.

In the survey of undergraduate education in allergy, the principal findings in the questionnaires answered by the deans of the medical school or by a member delegated to answer the questionnaire were as follows:

More than one-third of the medical schools give no courses in allergy.

Only twelve of the seventy medical colleges have been approved for residencies and fellowships in allergy by the American Board of Medical Specialties.

Thirty-one medical schools have no funds available for research in allergy.

Thirty-four medical schools have increased instruction in allergy in

This survey was made possible by two grants of $2,000 each from the New York Community Trust.

Dr. Baldwin is president of the American Foundation for Allergic Diseases.

the last five years, but thirty-three have not. (Three institutions did not answer this question.)

Departmental teaching staffs specializing in the allergic diseases vary from none in four schools to fifteen in one. About half of the seventy institutions have three or more staff members specializing in allergy.

All but five of the schools have allergy clinics and fifty-nine of the seventy use the clinics for teaching purposes. Most of the schools provide opportunities for working in wards or outpatient allergy clinics.

The following comments occurred most frequently in this set of questionnaires:

"The curriculum of the average medical school is so full that not enough time can be allotted for the presentation of all the fundamental material in the field of allergy."

"More time should be provided for the student to attend clinics in allergic disorders."

"More scholarships for undergraduate research in allergy should be provided."

"More physicians devoting full time to allergy should be added to the teaching staffs."

There were five expressions of opinion that allergy should not be made a specialty but that its teaching should be woven into the basic instruction of the department concerned; i.e., medicine, pediatrics, dermatology, otorhinopharyngology, and psychiatry.

The results of the second survey, representing opinion of medical students, followed much the same pattern. Sixteen of the Alpha Omega Alpha chapters reported that no courses in allergy were given at their institutions. Forty of the forty-three responding said their institutions had allergy clinics, but only twenty-eight of these reported that undergraduate instruction in allergy included clinical training. The opportunity to work in wards or outpatient clinics was reported as available in thirty-three of the forty-three institutions.

Estimates of the thoroughness of instruction in allergy, as expressed by the medical students, were mainly critical. In only five institutions was instruction considered adequate. In five others it was rated "moderate" and in seventeen additional institutions inadequate.

The students made the following suggestions for the improvement of undergraduate training in allergy:

Increased opportunities to work with patients afflicted by allergic disorders.

More full-time allergists on teaching staffs and more instruction in basic principles of allergy.

Establishment of separate department of allergy.

Provision of research fellowships for students interested in allergy at the undergraduate level.

In his "Report on a Survey of Graduate Education in Allergy," Dr. Kern traces development of teaching facilities for the training of

allergists and states that "The adequacy of the supply of allergists for practice and research depends upon the availability of adequate number of training stations and programs of sufficient merit to attract trainees." He mentions a survey conducted in 1949 and its findings to the effect that at that time 20 per cent of the residencies and fellowships in allergy were vacant and that a number of institutions complained of difficulty in getting high grade men for allergy residencies and fellowships. The reasons for this difficulty included ignorance of the opportunities available for research and clinical training and the failure of the facilities to attract. "But more significant," states Dr. Kern, "is the suggestion that medical schools underemphasize the importance of allergic disease and that few hospitals rotate their interns and assistant residents through the allergy clinic. These difficulties still obtain: they are the more significant since training in allergy must rest on the broader base of training in internal medicine or pediatrics."

Dr. Kern then proceeds to list the replies to the questionnaire. His analysis indicates that since 1949 there has been an increase in the total number of allergy residencies and fellowships (forty compared to thirty-one), an increase in approved residencies and fellowships (thirty-four versus twenty-four), an increase in institutions with such programs (twenty-four versus seventeen), and an increase in institutions with approved programs (eighteen versus twelve).

With regard to graduate training of specialists in internal medicine and pediatrics, Dr. Kern states that it is axiomatic that the properly trained internist or pediatrician must have some factual knowledge of the clinical manifestations of allergy, their recognition and their management. Therefore, it should be required that residency training in these two fields (internal medicine and pediatrics) include the routine assignment of trainees to a period of service in the allergy clinic of the hospital, for experience with allergic patients, by far the greater number of whom are ambulatory. Dr. Kern's analysis of the questionnaire in this regard concludes "it is clear that this phase of training in allergy is being seriously neglected."

Dr. Kern devotes a considerable portion of his analysis to a criticism of the present questionnaire because he is convinced of the great need of a better and expanding program in the graduate training of specialists and the postgraduate education of many physicians in the field of allergy and because he feels that the present survey with all its shortcomings has been a valuable step forward in this direction. He therefore outlines a new and continuing program for "Future Surveys and the Encouragement of More Opportunities for Graduate and Postgraduate Training and Research in Allergy."

This whole matter is laid out with great care and detail, and should be most valuable as a plan for further surveys in this direction. Dr. Kern concludes his analysis as follows:

Speaking of the importance of future surveys, he states "The agency

which has gathered, studied and evaluated comprehensive information on programs of education and research in allergy is in the best possible position to judge where financial and other assistance could foster these programs. Moreover, the agency which possesses this knowledge will best command the approval and support of all who wish the cause of allergy well and who are seeking an agent to mediate their benefactors. Therefore, the American Foundation for Allergic Diseases should find its greatest challenge to service in the subvention of research in allergy, promotion of graduate and postgraduate education and the more effective enlistment of funds from the friends of allergy the better to perform that service."

The grants supplied by the New York Community Trust have materially helped to emphasize the needs in undergraduate and graduate medical education in allergy, and to point the way to future progress in this area. As president of the American Foundation for Allergic Diseases, speaking for the trustees and the membership of the Scientific and Educational Council, I want to express our gratitude to the New York Community Trust for having made this study possible.

SURVEY OF UNDERGRADUATE EDUCATION IN ALLERGY

Analysis of the Questionnaires Answered by the Deans of Medical Schools

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THERE were seventy questionnaires returned from the medical schools. In three instances, two questionnaires were received from the same school; i.e., the University of Minnesota and the Los Angeles University each reported from the school of medicine and also from the department of pediatrics, while one report was received from the New York University College of Medicine and one from the New York Postgraduate Medical School in Pediatrics. Again, many of the reports were incomplete, and interpretations were necessary for some questions. A summary of the questionnaires is given in the accompanying table.

1. Only two (2.9 per cent) institutions reported having a separate department of allergy. Among the sixty-eight institutions, thirty-nine (55.7 per cent) included the department of allergy under the department of medicine. Another eighteen (25.7 per cent) had the department of allergy under both medicine and pediatrics. In one institution the department of allergy was under pediatrics; in another it was jointly under medicine and another department; in two more it was under each depart-

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SURVEY OF UNDERGRADUATE EDUCATION IN ALLERGY

1. Is there a separate department in your institution?
   Yes—1 No—59
   Under the Department of Medicine—47
   Under the Department of Pediatrics—12
   Other —None

2. What is the length of the prescribed courses in allergy?

None:	24				
Included in other courses:	3	12 hours:	1	36 hours:	1
3 hours:	1	13 hours:	1	3 weeks:	1
5 hours:	1	16 hours:	2	1 month:	1
6 hours:	2	17 hours:	1	9 weeks:	1
7 hours:	1	19 hours:	1	3 months:	1
8 hours:	1	20 hours:	2	3-4 years:	1
10 hours:	1	26 hours:	1	Elective medicine:	12 weeks
11 hours:	1	28 hours:	1	Required pediatrics:	6 weeks

3. Is there an allergy clinic?
   Yes—50 No—5

4. How long has it been operating?

0- 5 years	8	10-20 years	16
5-10 years	4	20 or more	22

5. Has the clinic been approved for residency and fellowships in allergy by the American Board of Medical Specialties?
   Yes—7 No—47

6. Is the clinic used for teaching?
   Yes—42 No—10
   If so, do all the students rotate through it? 28
   Or is it elective? 9
   Assigned 1

7. How many members of your departmental teaching staff have their chief interest in allergy?

0- 4	3- 8	6- 3	10- 2
1-14	4- 5	7- 1	
2-12	5- 3	8- 2	

   How many others in the institution have a major research or clinical interest in allergy?

0-16	3- 2	6- 1
1- 5	4- 9	7- 1
2- 8	5- 5	

8. Do all students have clinical instruction in allergy by allergists?
   Yes—46 Elective—1 No—7
   If yes, how many hours?

3 hours	2			17 hours	1
4 hours	3			20 hours	4
6 hours	3			22 hours	1
7 hours	3			27 hours	1
8 hours	2			28 hours	1
9 hours	1			33 hours	2
10 hours	3			36 hours	1
11 hours	1			45 hours	1
12 hours	4	(pediatrics)	1	48 hours	1
16 hours	2			3 weeks	1
				variable	3

9. Does this include the opportunity to work in wards or out-patient clinics?
Yes—40 Wards—12 Out-patient—19 Occasionally—1 No—9

10. Are funds provided for research in allergy?
None—27 Institutional—9 Private—11 Gov't—7 Foundations—8 Industry—6

11. Are funds provided for research in related fields?

None	2	Dermatology	33
Immunology	38	Pharmacology	37
Microbiology	38	Physiology	38
Pathology	37		

12. What proportion of these funds in related fields is used for problems bearing on allergy?

None	13	10 %	1
No exact estimate	20	20 %	1
Variable	1	33⅓%	2
Very little	7	100 %	1
5%	1		

13. Has instruction in allergy increased during the last five years?
Yes—27 No—26 Decreased—1

ment in the institution. There were three institutions in which no assignment was made, and in four others the question was left unanswered.

2. Of the seventy institutions, twenty-six (37.1 per cent) indicated that no course was given. Twelve institutions failed to answer the question. The remaining thirty-two institutions reported the length of their courses in hours (from four to twenty-eight), weeks (three to ten), months (one to three), lectures (three to seven), and years (one institution reported three to four years).

3. Only five (7.1 per cent) of the institutions failed to have an allergy clinic.

4. Twenty-eight (43.1 per cent) of the institutions have been operating their allergy clinics for more than twenty years, while another twenty (30.8 per cent) institutions have been operating between ten and twenty years. Another six institutions have been operating between five and ten years, while five institutions reported less than five years. In four instances, the reports were not classifiable, and two institutions failed to answer the question.

5. Only twelve (17.2 per cent) of the seventy institutions reported as having been approved for residency and fellowships in allergy by the American Board of Medical Specialties. Fifty-two institutions reported they had not been approved, and six institutions failed to answer the question.

6. Most of the institutions, fifty-nine (84.3 per cent), used the clinic for teaching. Eight institutions reported that they did not use the clinic for teaching, and three institutions failed to answer the question. Of the fifty-nine institutions using the clinic for teaching, forty-three (72.9 per cent) rotate their students, and in eleven (18.6 per cent) the situation

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Survey of Undergraduate Education in Allergy

Summary of 70 questionnaires answered by the Deans of Medical Schools

1. Part 1 Yes—2 No—68
   Part 2 Med.—39 Med. and Ped.—18 Med. and other—1 Ped.—1
   Within each dept.—2 None—3 Not stated—4

2.

None	26	12 hours	2	9 weeks	2	3 lectures	1
4 hours	1	19 hours	1	10 weeks	1	5 lectures	1
6 hours	3	20 hours	2	1 month	1	7 lectures	1
8 hours	2	28 hours	1	3 months	1	Varying lectures	
10 hours	1	3 weeks	2	3-4 years	1	and clinics	5
11 hours	1	6 weeks	2			Not stated	12

3. Yes—65 No—5

4. 0-4 yrs.—5 5-9 yrs.—6 10-19 yrs.—20 20-28 yrs.—4 not stated—2

5. Yes—12 No—52 Not stated—6

6. Part 1 Yes—59 No—8 Not stated—3
   Part 2 Rotate—43 Elective—11 Assigned—1 Not stated—4

7.

Part 1	0- 4	5-4		13-	1
	1-15	6-4		15-	1
	2-14	7-1		Several	1
	3-11	8-2		Not stated	3
	4- 6	10-3			
Part 2	0-19	4-8		Several	4
	1- 5	5-5		Not stated	15
	2- 9	6-1			
	3- 3	7-1			

8. Part 1
   Yes—61 No—7 Elective—1 Not stated—1

Part 2	2 hours	2	10 hours	4	24 hours	2
	3 hours	2	11 hours	1	27 hours	1
	4 hours	1	12 hours	6	28 hours	1
	5 hours	3	15 hours	1	33 hours	2
	6 hours	7	16 hours	2	45 hours	1
	7 hours	2	18 hours	4	2 days	1
	8 hours	4	20 hours	1	varies	5
	9 hours	4	22 hours	2	not stated	5

9. Yes—57 No—8 Elective—1 Not stated—4

10.

Institutional	(1)—2	(1)	(2)—3	(1)	(2) (4)—1
Industry	(2)—3	(1)	(4)—2	(1)	(2) (5)—1
Government	(3)—2	(1)	(5)—1	(1)	(2) (5)—1
Private	(4)—5	(3)	(4)—1	(1)	(3) (5)—1
Foundations	(5)—1	(4)	(5)—1	(2)	(3) (5)—1

All—2
Total—30
No—31
Not stated—9

11. Part 1 Yes—60 No—6 Not stated—4

Part 2	Immunology	41	Pathology 37
	Microbiology	41	Dermatology 33
	Physiology	40	Not specified 9
	Pharmacology	39	

12.

None	11	20%	1
Little	12	33%	1
5 %	2	No estimate	25
10%	2	Not stated	5

13. Yes—33 No—34 Not stated—3

is elective. In one institution the students are assigned, and four institutions failed to answer the question.

7. The number of members of the departmental teaching staff whose chief interest was in allergy varied from none in four institutions to fifteen in one institution. One institution reported "several" and three institutions failed to answer the question. It is of interest to note that approximately one-half of the seventy institutions reported that three or more members of their staff had their chief interest in allergy. About half (thirty-six out of seventy) of the institutions reported that other members of their faculty had a major research or clinical interest in allergy. Ninteen institutions reported none, and fifteen institutions failed to answer the question.

8. The number of hours of instruction ranged from two to forty-five, with thirty-five (50 per cent) of the institutions reporting seven or more hours. In five institutions, their reports were not classifiable, and five more institutions failed to answer the question.

9. Most of the institutions, fifty-seven (91.4 per cent) provided the opportunity to work in wards or outpatient clinics. One institution reported "elective" and eight institutions said no. There were four institutions that failed to answer the question.

10. There were nine institutions that did not answer the question whether or not funds are provided for research in allergy. Thirty-one institutions reported that no funds are provided. The remaining thirty institutions (42.9 per cent of the seventy) received funds from various sources. Only two institutions received funds from all five classes—institutional, industry, government, private, and foundations. Six institutions received funds from three of the five classes, eight from two classes, and thirteen from just one source.

11. Funds are provided for research in other related fields in sixty (85 per cent) institutions. Six institutions reported that no funds are provided, and four institutions failed to answer the question. Nine of the sixty institutions failed to specify which of the related fields received funds. A number of institutions received funds assigned to certain departments as follows: immunology, forty-one; microbiology, forty-one; physiology, forty; pharmacology, thirty-nine; pathology, thirty-seven; and dermatology, thirty-three.

12. In answer to the question as to what proportion of these funds in related fields is used for problems bearing on allergy, twenty-five of the sixty institutions commented but gave no estimate, and five institutions failed to answer. Twelve institutions said that none of the funds were used in this manner. Of the eighteen institutions that gave an estimate, six indicated 5-32 per cent, while twelve others reported "little."

13. There were thirty-four institutions reporting an increase in instruction in allergy during the past five years, thirty-three institutions indicating no increase and three did not answer the question.

14. Because of the nature of question 14, the answers are too general to lend themselves readily to statistical appraisal.

15. The same may be said of answers to question 15, although the following general comments occur most frequently: (a) the curriculum of the average medical school is so full that not enough time can be allotted for the presentation of all the fundamental material in the field of allergy (b) more time should be provided for the student to attend clinics for allergic disorders; (c) more scholarships for undergraduate research in allergy should be provided; (d) more physicians devoting full time to allergy should be added to the teaching staff; (e) some (at least 5 per cent) expressed the opinion that allergy should not be made a specialty but that its teaching should be woven into the basic instruction of the department concerned—medicine, pediatrics, dermatology, otorhinopharyngology, psychiatry.

SURVEY OF UNDERGRADUATE EDUCATION IN ALLERGY

Analysis of the Questionnaires Answered by Medical School Student Members of Alpha Omega Alpha Chapters (Honorary Medical School Fraternity)

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THIRTY-FOUR questionnaires were returned by Alpha Omega Alpha Chapters. In a few instances not all the questions were answered, and on some questions the answers were not definite. A summary of the data for each question is given below:

1. In only four (9.3 per cent) of the forty-three institutions was there a separate department of allergy. Among the remaining thirty-nine institutions, six (15.4 per cent) stated that the courses were taught in each department. In most institutions, thirty-one (79.4 per cent), the department of allergy was under the department of medicine distributed as follows: twenty-two (56.4 per cent) directly, seven (17.9 per cent) with pediatrics, and two (5.1 per cent) with other departments. In one institution the department of allergy was directly under the department of pediatrics, and in another institution the responsible department was not given.

2. Of the forty-three institutions, sixteen (37.2 per cent) indicated that no course was given. The length of the prescribed courses varied with each institution, from occasional lectures to an integrated program over a four-year period.

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3. Only three (7.0 per cent) of the institutions failed to have an allergy clinic.

4. Among the forty institutions having an allergy clinic, twenty-eight (70 per cent) reported that their course in allergy included clinical training. Two institutions had no undergraduate training, in one institution the training was optional, and in nine (22.5 per cent) no clinical training was included.

The length of the course varied considerably with the institutions. Often the number of hours per week was given, but the number of weeks or length of the course was omitted. Although not definite, the shortest course probably totaled eight hours, and the longest forty-four hours. Five institutions reported two hours per week, five reported three hours per week, six reported four hours per week, and the others reported variable periods such as one week or thirty hours per year.

5. In thirty-four institutions (79.1 per cent) the clinical instruction in allergy is supervised by allergists. Five institutions used other personnel and in four institutions no clinical instruction was given.

6. The opportunity to work in wards or outpatient clinics was reported as available in thirty-three (76.7 per cent) of the forty-three institutions. One institution afforded the student observation privileges, another institution reported the opportunity as incidental, and in eight institutions the answer was no.

7. The question relating to the opportunity provided to conduct research in other related fields was not answered by three of the institutions. Among the forty answering, twenty-eight (60.0 per cent) answered yes, sixteen (27.5 per cent) said no, and five (12.5 per cent) provided the opportunity as an elective during the summer.

8. The institutions were asked to give an estimate of the thoroughness of the instruction in allergy, both didactic and clinical. The reports were not stereotyped, thus an interpretation was necessary in many instances. A summary of the findings is as follows. In only five institutions (11.6 per cent) was the instruction considered adequate for both didactic and clinical. In five (11.6 per cent), instruction could be classified for both as moderate, and in seventeen (39.5 per cent) the instruction was considered inadequate in both didactic and clinical. In sixteen institutions, eleven (25.6 per cent) considered their didactic instruction as adequate, and five considered their clinical instruction as adequate.

9. The question, "Have you additional suggestions for the improvement of undergraduate training in allergy?" brought forth almost as many answers as questionnaires. The following are representative of the group: (1) increased opportunities to work with patients afflicted by allergic disorders, either in the allergist's office one or two days a week, in the allergy ward of the hospital, or in allergy clinics; (2) more full-time allergists on the teaching staff; (3) more instruction in the

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Survey of Undergraduate Education in Allergy

Summary of 43 Questionnaires Answered by Medical School Students
Who Are Members of Alpha Omega Alpha Chapters

(Honorary medical school fraternity)

1. Part 1 Yes—4 No—39
   Part 2 Med.—22 Med. and Ped.—7 Med. and other—2, Ped.—1
   None—6 Other—1

2. None	16	2 weeks	1	Occasional lectures	4
5 hours	1				
8 hours	2	4 weeks	1	Lectures, 2 yrs.	2
10 hours	2	10 weeks	1	Lectures, 2 wks.	1
12 hours	1	16 weeks	1	Lectures jr. yr., out-patient sr. yr.	2
1-4 hours	1	9 months	1	2 lectures, 10 after clinic	1
3¼ hours	1	1 wk. for 6 wks.		2 integrated over 4 yrs.	1

3. Yes—40 No—3

4. Part 1 Yes—28	No—9	Optional—1	No undergrad. trng.—2
Part 2	2 hours	5	1 week 1
	2-3 hours	2	16 hours/year 1
	3 hours	5	24 hours/year 1
	4 hours	6	30 hours/year 1
	6 hours	2	24 hours in 2 weeks 1
	12 hours	1	Indefinite 2

5. Yes—34 No—5 No clin. instr.—4

6. Yes—33 No—8 Observe—1 Incidental—1

7. Yes—24 No—11 Summer elective—5 Not stated—3

8. Didactic	Adequate	11	Inadequate	5	Moderate	0
Clinical	Adequate	5	Inadequate	10	Moderate	1
Both	Adequate	5	Inadequate	5	Moderate	5

Addendum 1 to the Survey of Undergraduate Education in Allergy

1. Is there a separate department in your institution? Yes—1 No—12
   Under the Department of Medicine 12
   Under the Department of Pediatrics 6

2. What is the length of the prescribed courses in allergy?

None	5	13 hours	1	6 weeks	1
4 hours	1	15 hours	1	10 weeks	1
6 hours	1	22 hours	1	1—See Univ. of Calif. Med. Center	

3. Is there an allergy clinic? Yes—13

4. How long has it been operating?

10 years	1	20 years	2	28 years	1
12 years	1	23 years	1	30 years	1
15 years	2	25 years	3		

5. Has the clinic been approved for residency and fellowships in allergy by the American Board of Medical Specialists? Yes—4 No—9

6. Is the clinic used for teaching? Yes—13
   If so, do all students rotate through it? 9
   Or is it elective 3
   No answer 1

7. How many members of your departmental teaching staff have their chief interest in allergy?

1-1	3-3	1-5	1-13
2-2	1-4	1-6	1-15

   How many others in the institution have a major research or clinical interest in allergy?

None 7	1-2	1-4
1 1	1-3	1-5

8. Do all students have clinical instruction in allergy by allergists? Yes—12 No 1
   If yes, how many hours?
   2 hours 1 12 hours 1 15 hours 1 20-24 hours 3
   10 hours 2 13 hours 1 16 hours 1
9. Does this include the opportunity to work in wards or outpatient clinics?
   Yes 9 No 1 Outpatient 3
10. Are funds provided for research in allergy?
    None 5 Institutional and government 2
    Private 2 Industrial, institutional and foundation 1
    Institutional, government and private 1
    Research grants to staff 1
11. Are funds provided for research in other related fields?
    None 3 Dermatology 4 Yes 1
    Immunology 6 Pharmacology 5
    Microbiology 5 Physiology 5
    Pathology 5
12. Has instruction in allergy increased during the last five years?
    Yes 6 No 5

basic principles of allergy (Some feel it is not possible to increase lectures in allergy because the medical curriculum is already too crowded.); (4) establishment of a department of allergy in the medical school (There is some difference of opinion as to whether this should be separate from or part of the department of internal medicine.); and (5) provision of research fellowships for those interested in allergy at the undergraduate level. A few institutions said no, and several failed to answer.

REPORT ON A SURVEY OF GRADUATE EDUCATION IN ALLERGY

As Conducted by The American Foundation for Allergic Diseases

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THE performance of a survey is proof that there exists a formal program for the training of allergists. The word "allergy" is only forty-nine years old, the practice of clinical allergy dates only to about 1911, and the inclusion of this subject in an occasional medical curriculum had its beginnings about five years later.

Since then, allergy has become a routine part of the teaching program of all medical schools, beginning with the basic science years in the course of immunology, and continuing in the clinical years by formal lectures and by practical instruction in the outpatient clinic and at the bedside. Medical textbooks all carry sections devoted to allergy, and, in addition, there are increasing numbers of texts on allergy written for students.

The chief evidence of the importance and scope of clinical allergy lies in its recognition by certain American certifying boards (medicine, pediatrics) as a *subspecialty* in those fields worthy of certification, after

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basic certification; for example in medicine, when the physician has shown himself proficient in allergy upon formal examination. Such certification by the American Board of Internal Medicine began in 1936.

The first allergists were the pioneers in the field. They, in turn, trained additional associates by years of apprenticeship in clinic and laboratory. They, too, were responsible for introducing the subject of allergy into the curricula of our medical schools. Indeed, in 1935, when Tumpeer[3] surveyed the teaching of allergy to undergraduates, he found that the emphasis which this subject received was largely the product of the personality and enthusiasm of these pioneers.

An important early means for instruction as well as interchange of ideas was found in the societies, national and local, devoted to the field of allergy. A valuable early contribution of the first two national societies (Society for the Study of Asthma and Allied Conditions, Association for the Study of Allergy) was the formulation of standards upon which to base the approval of allergy clinics, not only for the sound practice of allergy, but especially for the training of would-be allergists. Thus were laid the foundations that made possible the program of certification above mentioned.

Certification in allergy therefore predicates not only the existence of standards for the training of allergists, but also the existence of teaching programs in recognized and approved facilities where such training may be obtained.

The adequacy of the supply of allergists for practice and research depends upon the availability of adequate numbers of training stations and programs of sufficient merit to attract trainees. In a survey conducted in 1949, and reported in an editorial in the *Annals of Internal Medicine*, Baldwin and Spain[1] listed a total of thirty-one residencies and fellowships offered in seventeen institutions, of which one was federal and sixteen nonfederal. Of the nonfederal institutions, fifteen were in hospitals affiliated with medical schools, and one (Montefiore, Pittsburgh) was in a nonteaching hospital. Of the thirty-one residencies and fellowships listed in 1949, six were vacant (20 per cent). While this percentage of vacancies was not out of line with data for residencies in other fields, any vacancy in an allergy residency is regrettable when trained allergists are so scarce. One must therefore mention the comment of Baldwin and Spain that eight institutions complained of difficulty in getting high-grade men due to ignorance of the opportunities available for research and clinical training and the failure of present facilities to attract. But more significant is the suggestion that medical schools underemphasize the importance of allergic diseases and that few hospitals rotate their interns and assistant residents through the allergy clinic. These difficulties still obtain; they are the more significant since training in allergy must rest on the broader base of training in internal medicine or pediatrics.

By no means all who seek instruction in allergy do so because they

hope to qualify as allergists. Many physicians, especially general practitioners, realize the inadequacy of their earlier teaching and are eager for "refresher" courses. This type of instruction, while less formal and, because of its manifold origins and sponsorships, elusive of critical evaluation, is nevertheless an important phase of postgraduate education in allergy.

The present survey deals primarily with the more formal aspects of the training of allergists. Information for the survey was gathered by the American Foundation for Allergic Diseases by means of a questionnaire sent to all the medical schools in the United States and to certain other institutions in which it was known that some type of graduate instruction in allergy was being conducted. The resultant replies were turned over for analysis and evaluation to the writer of this report, who took no active part in the planning and execution of the survey, except to communicate with a few schools from which he knew the data to be grossly inadequate.

This report consists of four parts:

1. The analysis of the replies to the questionnaires.
2. A review of the latest published data on allergy training facilities as shown in the list of approved residency training programs in the Internship and Residency Number of the *Journal of the American Medical Association,* September 24, 1955.
3. A critique of the survey.
4. Some speculation on how to extend and make more effective the facilities for formal training in allergy.

ANALYSIS OF REPLIES TO QUESTIONNAIRES

There are listed in Table I the eighty-one medical schools in the United States and the four additional insittutions from which replies were received. They are arranged by states in alphabetical order, the schools in the order listed in the *Journal of the American Medical Association.*

The information on graduate instruction in allergy is listed in three columns: (1) Formal training by residency or fellowship, to prepare the physician for certification as a specialist; (2) rotation of residents (especially those in medicine and pediatrics) through the allergy clinic to give them an insight into the role of allergy in general medical experience, and perhaps to arouse an interest in allergy as a specialty; and (3) courses to serve as "refreshers" for physicians in general practice or in a special field other than allergy. When an institution offers no instruction in any of these three categories, it is listed as having "No Program" (last column).

Before discussing the data set forth in Table I, one must first point out certain weaknesses, one in the questionnaire and the other in the technique of the survey. Other defects will be mentioned in Part III of

TABLE I. DATA FROM RETURNED QUESTIONNAIRES

School	Existing Residency or Fellowship	Rotation of Residents Through Allergy Clinic	"Refresher" Courses	No Program
1. Medical College of Alabama	none	none	none	X
2. University of Arkansas	no reply			
3. College of Medical Evangelists	no reply			
4. U. Southern Calif. School of Medicine	none	none	none	X
5. Stanford U. School of Medicine	none	none	none	X
6. U. Calif. School of Med. San Francisco	1 one-year traineeship now in preparation	none	none	
7. U. California School of Med. Los Angeles	none	Yes: internes and residents in Pediatrics	none	
8. U. Colorado School of Medicine	none	none	none	X
9. Yale University School of Medicine	none	none	none	X
10. Georgetown U. School of Medicine	none	none	none	X
11. Geo. Washington U. School of Medicine	none	none	"sometimes" 3-6 lectures in annual PG refresher course	
12. Howard U. College of Medicine	none	Pediatric residents, not Medicine or Dermatology	none	
13. Emory U. School of Medicine	no reply			
14. Medical College of Georgia	none	none	none	X
15. Chicago Medical School	none (a "research fellow")	none	none	X
16. Northwestern U. Medical School	2 one-year fellowships, Board approved	none	none	
17. Stritch School of Med. Lovola U.	none	none	none	X
18. U. of Chicago, School of Medicine	none	3-6 mos. in allergy as elective in residencies	none	
19. U. of Illinois, Col. of Medicine	2 one-year fellowships, Board-approved	none	none	
20. Cooke County Graduate School of Med.	none	none	Refresher courses: 1 mo. & 6 mos. for GP's	
21. Indiana U. School of Medicine	no reply			
22. State U. of Iowa College of Medicine	none	Each 3-yr. medical resident 2 mos. Allergy Clinic	none	
23. U. of Kansas School of Medicine	none	none	"an occasional PG course"	
24. U. of Louisville School of Medicine	none	none	none	X
25. La. State U. School of Medicine	none	none	none	X
26. Tulane U. of La., School of Medicine	none	Elective for Residents	none	
27. Johns Hopkins U. School of Medicine	No residency. 1 one-year Research Fellowship not Board-approved	Elective for Residents. Also: twice a year, a 6 mo. Resident from USPHS Hosp., (Baltimore)	none	
28. U. of Maryland School of Medicine	none	none	none	X
29. Boston University School of Medicine	none	none	none	X
30. Harvard Medical School	No reply (But M.G.H. has 1 one-yr. residency, Board-approved)			
31. Tufts College Medical School	no reply			
32. U. of Michigan Medical School	No reply (But U. Hosp. has 3 one-yr. residencies Board-approved)			

TABLE I. DATA FROM RETURNED QUESTIONNAIRES (Cont'd.)

School	Existing Residency or Fellowship	Rotation of Residents Through Allergy Clinic	"Refresher" Courses	No Program
33. Wayne U. College of Medicine	no reply			
34. U. of Minnesota Medical School	none	All Fellows in Medicine are 3 mos. in Allergy Clinic	occasional	
35. U. of Mississippi School of Medicine	none	none	none	X
36. U. of Missouri School of Medicine	no reply			
37. St. Louis U. School of Medicine	no reply			
38. Washington U. School of Medicine	none	Residents in Medicine rotate once a week for 6 weeks	none	
39. Hansel Foundation St. Louis	none	none	1 week annually (ENT)	
40. Creighton U. School of Medicine	none	none	none	X
41. U. of Nebraska College of Medicine	no reply			
42. Dartmouth Medical School	none	none	none	X
43. Albany Medical College	none	none	none	X
44. U. of Buffalo School of Medicine	1 one-yr. Fellowship not approved 3 half days clinic 3 half days office	none	none	
45. Columbia U. College of P. & S.				X
(a) Presbyterian Hosp.	none	none	casual for M.D's in clinic	
(b) Roosevelt Hosp.	none (But AMA lists 4 approved one-yr. residencies)	none	none	
46. Cornell U. Medical College	none (1 part-time research fellow)	none	none	X
47. N. Y. Medical Col., Flower & Fifth Ave. Hospitals	no reply			
48. N.Y.U. College of Medicine	No reply (But AMA lists 2 one-yr. approved Res. at Bellevue)			
49. State U. of N.Y. Col. of Med. N.Y.C.	None (But AMA lists 1 one-yr. approved Res. Jewish Hospital)	none	occasional for G.P's	
50. State U. of N.Y. Col. of Med. Syracuse	none	Elective for Medical Res.	none	
51. N. Y. Polyclinic Med. School & Hosp.	none	none	2 wks. twice yearly for GP's	
52. U. of Rochester School of M. & Dent.	no reply			
53. U. of North Carolina School of Med.	none			
54. Duke U. School of Medicine	No reply (But AMA lists 2 one-yr. approved residencies)			
55. Bowman Gray School of Med. of Wake Forrest College	no reply			
56. U. of North Dakota School of Medicine	no reply			
57. U. of Cincinnati College of Medicine	no reply			
58. Western Reserve U. School of Medicine	none	none	none	X
59. Ohio State U. Col. of Medicine	1 one-yr. residency, not yet approved. Require two years Med. Res.	none	none	

TABLE 1. DATA FROM RETURNED QUESTIONNAIRES (Cont'd.)

School	Existing Residency or Fellowship	Rotation of Residents Through Allergy Clinic	"Refresher" Courses	No Program
60. U. of Oklahoma School of Medicine	none	none	none	X
61. U. of Oregon Medical School	none	none	none	X
62. Hahnemann Med. Col. & Hosp. of Phila.				
(a) Hahnemann Hosp.	none	none	none	X
(b) Einstein Center (Northern Div.)	none	none	annual 15 days	
63. Jefferson Medical College of Phila.	none	none	none	X
64. Temple U. School of Medicine	1 one-yr. residency, Board-approved. Requires two yrs. Med. Res.	All Med. Res. (4 yearly) rotate in 3rd.	see 62 b	
65. U. of Pennsylvania School of Medicine	1 one-yr. residency not yet approved	Elective for Medical residents	none	
66. Woman's Medical College of Penna.	none	none	none	X
67. U. of Pittsburgh School of Medicine	none	none	annual, 1 wk. for GP's	
68. Montefiori Hospital Pittsburgh	2 one-yr. Res. Board-approved	none	none	
69. Medical College of South Carolina	none	none	none	X
70. U. of So. Dakota School of Med. Sci.	no reply			
71. U. of Tennessee College of Medicine	no reply			
72. Meharry Medical College	no reply			
73. Vanderbilt U. School of Medicine	none	none	none	X
74. U. of Texas Southwestern Med. School	none	none	none	X
75. U. of Texas School of Medicine	none	none	occasional in Pediatric Allergy	
76. Baylor U. College of Medicine	none	Internes and Residents	none	
77. U. of Utah School of Medicine	no reply			
78. U. of Vermont College of Medicine	none	none	none	X
79. U. of Virginia Dept. of Medicine	3 one-yr. Res. Board-approved (also 1 one-yr. Research fellow)	none	none	
80. Medical College of Virginia	No reply (But one one-yr. res. listed by AMA. as approved			
81. U. of Washington School of Medicine	none	none	Every other year: 1 day	
82. West Virginia U. School of Medicine	no reply			
83. U. of Wisconsin Medical School	none	Medical Residents: 3 mos.	none	
84. Marquette U. School of Medicine	1 one-yr. residency, not approved	none	none	
85. U. of Puerto Rico School of Medicine	none	none	none	X

this report. The questionnaire was vague as to the type of information being sought. It gave the impression to some readers that the survey dealt with formal courses of instruction, and so the matter of residencies, although mentioned as a subtitle, was overlooked by some respondents. This could be confirmed by comparing the replies in the questionnaire with published data on approved residencies in allergy. The weakness in procedure was to send the questionnaire only to the office of the dean of a medical school and not to the chief of the allergy clinic as well. Some

deans failed to reply, yet there might be an approved residency in allergy in the school in question. Or a dean might overlook a residency in an affiliated teaching hospital. The best replies came when the dean referred the questionnaire for reply to the chief of an allergy section, and the best programs were noted when that chief had subspecialty certification in allergy in addition to basic certification in allergy or pediatrics.

Replies were received from fifty-seven of the eighty-one medical schools. No replies were received from the University of Arkansas, the College of Medical Evangelists, Emory School of Medicine, Indiana University School of Medicine, Harvard Medical School (yet there is a one-year residency in allergy approved by the American Board of Internal Medicine in the Massachusetts General Hospital, an affiliate of Harvard), Tufts College Medical School, University of Michigan Medical School (yet there are two approved one-year residencies in allergy in the University of Michigan Hospital), Wayne University College of Medicine, University of Missouri School of Medicine, St. Louis University School of Medicine, University of Nebraska College of Medicine, New York Medical College Flower and Fifth Avenue Hospitals, New York University College of Medicine (yet there are two approved one-year residencies in allergy in its affiliated Bellevue Hospital), University of Rochester School of Medicine and Dentistry, Duke University School of Medicine (yet there are two approved one-year residencies in allergy there), Bowman Gray School of Medicine of Wake Forest College, University of North Dakota School of Medicine, University of Cincinnati College of Medicine, University of South Dakota School of Medicine, University of Tennessee College of Medicine, Meharry Medical College, University of Utah School of Medicine, Medical College of Virginia (but there is an approved one-year residency in allergy there), and the West Virginia University School of Medicine. In short, five of the twenty-four schools that did not reply have a total of eight approved one-year residencies in allergy: Harvard, one; Michigan, two; New York University, two; Duke two; and the Medical College of Virginia, one. They and others may also have some other types of graduate training in allergy.

Of the fifty-seven replying schools, six have a total of thirteen American Board-approved one-year residencies in allergy. They are Northwestern, two; Illinois, two; Columbia, four; State University of New York College of Medicine, New York City, one; Temple, one; and the University of Virginia, three. Also the Montefiore Hospital of Pittsburgh has two such approved one-year residencies. Then, there are six medical schools which report a one-year fellowship or residency in existence, although not yet appproved: University of California School of Medicine in San Francisco, Johns Hopkins University, University of Buffalo, Ohio State University, the University of Pennsylvania, and Marquette University.

If we now sum up the information available on the eighty-one medical

schools and the four other institutions listed in Table I, on the basis of their replies *plus* the published data on approved programs in medical schools, we arrive at a figure of twenty-nine residencies (twenty-three Board-approved) in seventeen places (sixteen in medical schools), and all of them in nonfederal institutions. But this figure is still incomplete, as the next paragraph will show.

LATEST PUBLISHED DATA ON ALLERGY TRAINING PROGRAMS

The latest published data on allergy training programs approved by the American Board of Internal Medicine appeared in the *Journal of the American Medical Association,* September 24, 1955.[2] Here there are listed an additional eleven residencies, seven in federal hospitals, and four in the Mayo Clinic. The total number of residencies and fellowships for graduate training in allergy therefore appears to be forty, of which seven are in federal hospitals and thirty-three in nonfederal institutions.

It is of interest to compare the data of 1955 with those of 1949. For this purpose there have been combined in Table II the facts obtained in the present study and those gathered by Baldwin and Spain six years ago.

The significant evidences of progress are an increase in the total number of residencies and fellowships (forty compared to thirty-one), an increase in approved residencies and fellowships (thirty-four compared to twenty four), an increase in institutions with such programs (twenty-four compared to seventeen), and an increase in institutions with approved programs (eighteen compared to twelve).

Retrogression has occurred in some places. Four medical schools (Johns Hopkins University, Washington University, Cornell University, and Marquette University), which in 1949 each listed one residency (two of the four as "approved"— Johns Hopkins and Marquette), now have non- or none that are approved. One of the four (Cornell) has a part-time research fellowship that is now occupied by a man already certified in internal medicine and allergy. Another (Johns Hopkins), while it ha no *approved* residency in allergy at this time, does have a one-year fellowship in allergy for both clinical and investigative work in the allergy department, supported by funds under the control of the chief of the allergy clinic. At Washington University, where a non-approved residency was listed in 1949, there is now no residency, due to the fact that no chief of the allergy division has as yet been appointed to replace the former chief, a certified allergist, who had retired because of age. At Marquette University, an approved residency was listed in 1949; there is still a residency in allergy, but it does not have Board approval.

At this point, attention is called to two further aspects of the education of physicians with regard to allergy. The first has to do with the graduate training of specialists in internal medicine and in pediatrics. It is axiomatic

TABLE II. RESIDENCIES AND FELLOWSHIPS IN ALLERGY: COMBINED DATA OF 1955

(Questionnaire Answers and JAMA, 9/24/1955) and of 1949; and (Baldwin and Spain, Ann. Int. Med.)

Institution	1955		1949	
	No.	Board Approved	No.	Board Approved
FEDERAL				
1. U. S. Army Medical Center, Washington, D. C.	2	2	—	—
2. U. S. Naval Hospital, San Diego, Calif.	1	1	—	—
3. Veterans Administration Hospital, Long Beach, Cal.	1	1	—	—
4. Veterans Administration Hospital, Chicago, Ill.	1	1	—	—
5. Veterans Administration Hospital, Pittsburgh, Pa.	2	2	2	2
NON-FEDERAL				
6. U. of California School of Med. San Francisco	1	—	—	—
7. Northwestern U. Medical School	2	2	2	2
8. U. of Illinois College of Medicine	2	2	4	4
9. Johns Hopkins U. School of Medicine	1	—	1	1
10. Harvard Medical School (Mass. General Hospital)	1	1	1	1
11. U. of Michigan Medical School	2	2	3	—
12. Mayo Foundation, Rochester, Minn.	4	4	—	—
13. Washington U. School of Medicine (Barnes Hosp.)	—	—	1	—
14. U. of Buffalo School of Medicine	1	—	—	—
15. Columbia U. College of P. & S. (Roosevelt Hosp.)	4	4	2	2
16. Cornell U. Medical College (New York Hospital)	—	—	1	—
17. New York U. College of Med. (Bellevue Hospital)	2	2	2	2
18. State U. of New York College of Medicine N. Y. City (Jewish Hosp. Brooklyn)	1	1	3	3
19. Duke Univ. School of Medicine	2	2	1	—
20. Ohio State U. College of Medicine	1	—	—	—
21. Temple U. School of Medicine	1	1	—	—
22. U. of Pennsylvania School of Medicine	1	—	1	—
23. Montefiori Hospital, Pittsburgh	2	2	1	1
24. U. of Virginia Department of Medicine	3	3	3	3
25. Medical College of Virginia	1	1	2	2
26. Marquette U. School of Medicine (Milwaukee Co. Hospital)	1	—	1	1
Total Number of Residencies and Fellowships	40	34	31	24
Number of Institutions with Residencies or Fellowships	24		17	
Number of Institutions with APPROVED Residencies or Fellowships	18		12	

that a properly trained internist or pediatrician must have some practical knowledge of the clinical manifestations of allergy, their recognition and their management. Therefore, it should be required that residency training in these two fields include the routine assignment of trainees to a period of service in the allergy clinic of the hospital for experience with allergic patients, by far the greater number of whom are ambulatory. Yet, of the eighty-five institutions listed in Table I, only eight (University of California at Los Angeles, Howard University, State University of Iowa, University of Minnesota, Washington University, Baylor University, Temple University, and the University of Wisconsin) require residents (medical in six schools, pediatric in two) to serve a term of duty in the allergy clinic. In addition, such service is elective at five schools (University of Chicago, Tulane University, Johns Hopkins University, the State University of New York at Syracuse, and the University of Pennsylvania). Although there may be such training in the allergy clinics of schools that failed to reply, it is clear that this phase of training in allergy is being seriously neglected.

Then there is the matter of the postgraduate type of instruction in

allergy for practicing physicians, especially those in general practice, but also applicable to certified allergists requiring such instruction. Table I shows that twelve schools (George Washington University, Cook County Graduate School of Medicine, University of Kansas, Hansel Foundation, Columbia University, State University of New York in New York City, New York Polyclinic Medical School, Hahnemann Medical College, Temple University, University of Pittsburgh, University of Texas, and University of Washington) make some recurring effort in this direction by means of "refresher" courses. Here, too, the available information must be very incomplete. Nevertheless, there is great need for extension and expansion of such programs.

CRITIQUE OF THIS SURVEY

It is clear that the results of this survey are incomplete, defective, and fragmentary. In the hope that future attempts will give a more accurate picture of the status of graduate education in allergy, a searching critique of the present effort is indicated.

The questionnaire that was used has several obvious shortcomings. The greatest one lies in the assumption that a single-page form could possibly cover all the existing range of effort to teach allergy to physicians. This point will be elaborated in Part IV of this report, with suggestions for future procedure.

The questionnaire was not sufficiently clear to show the purpose for which it was intended. It bears the heading "Survey Graduate Education in Allergy." That can mean anything, from a single recurring lecture to some group of physicians, to the most formal and complete program of residency training of certifiable specialists in allergy. That the survey seeks information on formal training of would-be allergists is suggested by the subheading, "Fellowships and Residencies." Yet, at no later point in the form do the terms "fellowship" and "residency" occur.

The questionnaire fails to distinguish between graduate and postgraduate instruction. Graduate instruction refers to the formal and exhaustive training of graduate physicians especially with a view to their qualifying as specialists. Postgraduate education is not specifically so oriented; it may be a "refresher" course for those already certified as specialists in a field, or it may be an informative program to give men in general practice or in any specialty a new or better insight into a special field so that they may practice their own field more intelligently. In any case, postgraduate instruction is limited in the main to shorter periods, measured in days or weeks, whereas graduate instruction is carried out for a year or years. Yet the questionnaire begins with the one word "Graduate," and then asks questions about a *course* (hours? how often given? tuition fee?) that could only refer to a postgraduate type of instruction. No wonder the deans were confused and slurred over or omitted all

references to any formal graduate training by fellowship or residency in their schools and hospitals.

The questionnaire speaks of students and instructors, as if graduate instruction in allergy followed the same pattern as in an undergraduate department, with fixed curricular hours, lectures, classes, and demonstrations, but it asks nothing about the qualifications of the teachers (are they certified in medicine or pediatrics? and in the subspecialty, allergy?), or the prerequisites of training and background of those being instructed. Yet the American Boards have specifically defined these requirements of training for would-be residents in allergy as two years of residency training in medicine or pediatrics, or their equivalent.

The questionnaire asks in one line about "tuition fees," and then a few lines below about "scholarships" and sponsors, but makes no inquiry about stipends, subsistence, and other perquisites that so commonly pertain to fellowships and residencies. There resulted a few querulous replies about a need for funds to help trainees, but little or no information about the material things offered to trainees (such as published by the *J.A.M.A.* in its list of approved residency programs) which might well attract more and better applicants for training.

The lack of suitability of the questionnaire is best shown by the fact that of all the fifty-five that were returned, in only twelve was any attempt made to fill out the various rubrics; and in most of the twelve, as in all of the rest, the significant information was supplied not on the questionnaire but in an accompanying letter.

The questionnaire went into unnecessary detail in some regards in asking vaguely about "clinical and laboratory procedures," questions that should more properly be directed to the chief of a clinic seeking American Board approval for a residency program.

The questionnaire failed to ask for some important data. In addition to omitting reference to qualifications of instructors and trainees, it did not inquire about numbers of men in training or vacancies in existing residencies. It failed to ask about the rotation of interns and of residents in medicine, pediatrics, and others through the allergy clinic as part of their routine training. Indeed, it failed to ask about the existence of an allergy clinic. It failed to ask if interns and residents were given any instruction in allergy, practical experience with allergic patients, or under whose guidance this occurred.

This critique has been offered by the writer, not in a spirit of carping criticism, but because he is convinced of the great need of a better and expanding program in the graduate training of specialists and the postgraduate education of many physicians in the field of allergy, and because he feels that the present survey, with all of its shortcomings, has been a valuable step forward in this direction. He therefore ventures to outline a new and continuing program.

FUTURE SURVEYS AND THE ENCOURAGEMENT OF MORE OPPORTUNITIES FOR GRADUATE AND POSTGRADUATE TRAINING AND RESEARCH IN ALLERGY

Medical education in this country began in a very informal manner; a would-be student of medicine attached himself to a practicing physician and acquired his knowledge by day-to-day experience with patients as well as by the reading of textbooks. Long after medical schools were established, the preceptor type of program not only preceded a student's entry into medical school but supplemented the medical school training, whose sessions until around 1880 lasted only six months, October to April of each year. In recent years the merits of such a preceptorship have been rediscovered, so that a number of medical schools have adopted the plan of attaching senior students for a part of that year to men in general practice.

Preceptorship has always had its place in all phases of education and research, and it always will. This is particularly true in the beginnings of our knowledge about a new subject as introduced by a discoverer or a pioneer, and elaborated by him and the student he has inspired. Only when the topic has been sufficiently evolved and its content formalized does it find its place in a routine curriculum. The story of the science and practice of allergy is a relatively recent example of this process. Indeed, today there are many places—hospital clinics, laboratories, and physicians' offices—in which a preceptor type of training in allergy is being carried out and to good purpose. Where such training is being well performed, where clinical material is abundant, and where association with a formal teaching program is possible (for example, in a hospital associated or affiliated with a medical school, or in a hospital with an approved formal program of residency training), that which has begun as a preceptor program can and should be encouraged to improve itself to the point where its program meets the requirements prescribed by an American Board, and its trainees have the basic preliminary training and then such instruction in allergy that they can pass the examination for certification.

This encouragement must be the continuing function of some interested group, cognizant of the problems of graduate education in allergy and willing and able to help in their solution. The American Foundation for Allergic Diseases should begin such a program and should develop it until it may some day be turned over as a going concern to some agency of organized medicine or an interested medical society. At any event, it must be the project of a group that has the personnel, space, equipment, and money to keep it going. The cost of such a program should not be prohibitive. It would require the part-time help (less than half) of one secretary, a single filing cabinet, a postage bill of not over $300 a year and less than that for stationery. If a punch card system were employed,

the cost might be greater, but this would be offset by less time required of the personnel.

The basic function of such a "Program for the Study and Development of the Training of Allergists, the Continued Education of Physicians in Allergy, and the Fostering of Research in Allergy" are these:

1. It must have the facts on existing programs of graduate and postgraduate education in allergy.

2. It must keep that information up to date.

3. It must publish that information annually in journals that will make it available to those seeking instruction.

4. It should verify the information by periodic visits of inspection by qualified allergists to the institutions active in such education and research.

5. It should give advice, constructive criticism and encouragement, based on the knowledge of local programs, to help these to achieve and maintain the highest standards.

6. It should seek ways and means for financial and other assistance in the interest of supplying an adequate number of allergists and of fostering sound programs of research.

Each of these basic functions is discussed below.

1. Collection of information on graduate and postgraduate education in allergy. The first year there should go out a simple, clear questionnaire to gather certain elementary facts. The following questions should be included: Has your hospital an allergy clinic? Who is its physician-in-charge? Is he, or any physician on its staff, certified in allergy by an American Board? If your hospital has an allergy clinic, are your interns and the residents in medicine, pediatrics (or others) required to serve a tour of duty in the allergy clinic? If not required, may they elect such duty? If your hospital has no allergy clinic, how and by whom are your interns and residents instructed in the diagnosis and management of allergic diseases? Has your hospital a program of residency training in medicine and/or pediatrics approved by the American Board of Internal Medicine or of Pediatrics? What instruction in allergy do these residents receive? Has your hospital a residency or fellowship program in allergy? Has this program been approved by an American Board? How many residencies or fellowships in allergy are offered? How many of these are filled? How many vacant? What preliminary training do you require of such trainees in allergy? What stipend and perquisites pertain to a residency or fellowship in allergy? Does your hospital or school offer formal lecture or refresher courses in allergy to physicians? Please describe the number of hours, lectures, practical work in clinic or laboratory, and tuition fee. Does your allergy clinic carry on a research program?

The *first* questionnaire should be addressed to the following: (a) The deans of school of medicine; (b) the deans of graduate schools of medi-

cine; (c) the "Chief of the Allergy Clinic" in all general hospitals that have an AMA-approved internship program and a bed capacity of not less than 250 beds (there are about 500 such hospitals); (d) the "Chief of Medicine" in all hospitals with AMA-approved residencies in internal medicine (the *J.A.M.A.* lists 744 such hospitals); (e) the "Chief of Pediatrics" in all hospitals with the AMA-approved residencies in pediatrics (the *J.A.M.A.* lists 255 such hospitals); and (f) the "Chief of Medicine" in all hospitals with AMA-approved residencies in general practice (the *J.A.M.A.* lists 159 such hospitals). This list, of course, involves many duplications, but this will perhaps help to eliminate any omissions. What is more important, there is the greater opportunity that the questionnaire may arouse a lasting interest in the subject. After the first tabulation of the information from the questionnaires, there need be no further duplication.

The information so received should be transferred to cards and filed. Special colors of cards should be assigned to hospitals with approved residency or fellowship programs in allergy, to hospitals with existing but unapproved programs, to hospitals with no programs but with allergy clinics, and to those with neither allergy clinic nor program. A colored tab over the upper margin of the card could designate the hospital with a certified allergist on the staff. Tabs of other colors could designate those with a postgraduate or "refresher" program, and those with research activities. There should be a followup in each instance where the first questionnaire was not returned. Every questionnaire should be accompanied by a self-addressed and stamped envelope for its return.

2. In subsequent years the same basic questionnaire should be sent to new hospitals, or those newly reaching the 250-bed size, that appear in the *J.A.M.A.* issue on Internships and Residencies, and to the deans of new medical schools listed in the *J.A.M.A.* number on Medical Education.

In subsequent years each hospital in the file should receive a simple query: What change is there to report in your program of training and practice of allergy including the allergy clinic, the rotation of interns and residents through the allergy clinic, the residency or fellowship in allergy (approved or unapproved), the certification of an allergist on your staff, postgraduate "refresher" courses in allergy for physicians, and research in allergy?

Other questionnaires should be devised for further study of the problems of: (a) hospitals with an allergy residency program that has not yet been approved; (b) hospitals with certified allergists on the staff, but without training programs; and (c) hospitals with allergy clinics, but without training programs or certified allergists.

The details of these questionnaires cannot be stated at this time. In general, they should be prepared with a view to encouraging self-appraisal and improvement, and especially to seeking Board approval. At times

there is needed a letter from a member of the Foundation to a dean or a chief of medicine to support the cause of the allergist on his staff. A letter from the Foundation might also raise the hope of financial support for a good research program.

3. An annual report should be published in *The Journal of Allergy* and in the ANNALS OF ALLERGY. It should give such pertinent information as might be calculated to further the cause of education and research in allergy. This should certainly include a list of hospitals with approved and unapproved residencies and fellowships in allergy, their location, the chief of service, the number of residencies offered, the number filled in the current year, and the monthly stipend. There could also be a list of postgraduate refresher courses regularly offered, their essential content, the sponsoring hospital, the dates and hours scheduled, the number of students accepted, and the tuition fee. Then there could be a statistical section with data on the number of hospitals with allergy clinics, their numbers by states, the number of certified allergists attached, and such other information as may from time to time seem appropriate; for example, the research programs under subvention by the Foundation.

4. Periodic visits of inspection by qualified allergists to institutions with active programs in education and research in allergy would be of the greatest value, not only in verifying the data on such programs, but in studying local needs and in offering help and advice. The visitors should be certified allergists, themselves conducting approved educational programs, and living in the same geographical area as the hospital visited so that there would be a minimum of expense and travel costs. The visitors would serve without compensation. A reasonable degree of uniformity could be achieved by the use of a sufficiently detailed checklist of items to be noted by the visitors. Of particular importance would be the opportunity to assess the merit and needs of research activities.

5. Suitable advice, constructive criticism, and encouragement could best be formulated on the basis of reports of such visitors. This needs no elaboration here.

6. The agency which has gathered, studied and evaluated this comprehensive information on programs of education and research in allergy is in the best possible position to judge where financial and other assistance could foster those programs. Moreover, the agency which possesses this knowledge will best command the approval and support of all who wish the cause of allergy well and who are seeking for an agent to mediate their benefactions. Therefore, the American Foundation for Allergic Diseases should find here its greatest challenge to service in the subvention of research in allergy, promotion of graduate and postgraduate

education, and the more effective enlistment of funds from the friends of allergy to better perform that service.

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SURVEY ON EDUCATION IN ALLERGY

A Summary

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WITH the support of the New York Community Trust, the American Foundation for Allergic Diseases has recently completed surveys on education in allergy. One dealt with undergraduate facilities, the other with graduate and postgraduate facilities.

1. *Undergraduate Education.*—Returns from seventy medical schools were analyzed by Dr. Giles A. Koelsche, from whose report a summary of pertinent information has been drawn. This shows that over one-third of the schools reporting provide no allergy training, with twelve of the schools not reporting at all, in spite of the fact that all but five of the seventy reported that they have allergy clinics. Again, of the seventy institutions, only twelve reported that their allergy clinic was "approved" for residency or fellowship training by the American Boards.

One-half of the institutions reported that members of their faculty, other than those directly concerned with allergy, had some major research or clinical interest in the allergic problems. Again, in one-half of the institutions, instruction in allergy was limited to about seven hours altogether, although the opportunity was afforded by option to work in the clinic or the wards on allergy problems in 81 per cent, and, finally, funds for research in allergy from various sources existed in only forty-three of the reporting institutions, whereas in other special fields there were funds in 85 per cent. However, it is not clear from this report just what proportion of the latter funds in related fields might be working on problems directly or indirectly related to allergy. In one-half of the institutions reporting, there had been some, but slight, increase in allergy instruction over the past five years.

Dr. Cooke is Director, Institute of Allergy, Roosevelt Hospital, New York, New York. He has served as Chairman of the Scientific and Educational Council of the American Foundation for Allergic Diseases.

2. *Graduate and Postgraduate Education.*—The replies from eighty-five medical schools and institutions, to which were added some published data on approved programs, were reviewed by Dr. Richard A. Kern. Of particular interest are some of the comments of his analysis. For example, the total number of residencies and fellowships for graduate training appears to be forty (seven of them in federal hospitals), thirty-four of which in eighteen different institutions are "approved" by the American Boards. Dr. Kern further states: "The significant evidences of progress are an increase in the total number of residencies and fellowships (forty compared to thirty-one), an increase in approved residencies and fellowships (thirty-four compared to twenty-four), an increase in institutions with such programs (twenty-four compared to seventeen), and an increase in institutions with approved programs (eighteen compared to twelve). . . . At this point, attention is called to two further aspects of the education of physicians with regard to allergy. The first has to do with the graduate training of specialists in internal medicine and in pediatrics. It is axiomatic that a properly trained internist or pediatrician must have some practical knowledge of the clinical manifestations of allergy, their recognition and their management. Therefore, it should be required that residency training in these two fields include the routine assignment of trainees to a period of service in the allergy clinic of the hospital, for experience with allergic patients, by far the greater number of whom are ambulatory. Yet, of the eighty-five institutions listed in Table I, only eight (University of California at Los Angeles, Howard University, State University of Iowa, University of Minnesota, Washington University, Temple University, Baylor University, and the University of Wisconsin) require residents (medical in six schools, pediatric in two) to serve a term of duty in the allergy clinic. In addition, such service is elective at five schools (University of Chicago, Tulane University, Johns Hopkins University, State University of New York at Syracuse, and the University of Pennsylvania). Although there may be such training in the allergy clinics of schools that failed to reply, it is clear that this phase of training in allergy is being seriously neglected.

"Then there is the matter of the postgraduate type of instruction in allergy for practicing physicians, especially those in general practice, but also applicable to certified allergists requiring such instruction. Table I shows that twelve schools (George Washington University, Cook County Graduate School of Medicine, University of Kansas, Hansel Foundation, Columbia University, State University of New York in New York City, New York Polyclinic Medical School, Hahnemann Medical College, Temple University, University of Pittsburgh, University of Texas, and University of Washington) make some recurring effort in this direction by means of "refresher" courses. Here, too, the available information must be very incomplete. Nevertheless, there is great need for extension and expansion of such programs."

The Foundation plans to continue from time to time surveys with an improved questionnaire and with better techniques, following some of the excellent suggestions Dr. Kern has made. It is our hope that this brief summary of the recent surveys will provoke not only interest but some action on the part of medical schools, the deans and the professors of medicine and pediatrics, as well as the directors of institutions concerned with medical education, for it is evident that there is room for improvement in education in the field of allergy (sensitization) which is of great and growing importance to medicine.

NATIONAL FUND FOR MEDICAL EDUCATION

On April 15, H. Rowan Gaither, Jr., president of The Ford Foundation, announced a $10,000,000 program of grants to the National Fund for Medical Education to assist in its efforts to strengthen the financial support for medical schools, both public and private, throughout the United States and to develop new sources of such support. Grants from this appropriation will be paid to the National Fund on a matching scale in a program that could last up to ten years but which might be completed in five, depending on the rate at which additional support for medical education is developed by the National Fund. Only $2,000,000 will be granted in any one year. By adoption of the sliding formula, through which The Ford Foundation will match the National Fund's receipts, it is hoped that encouragement will be given, especially in the early years of the plan, to increasing the contributions of existing donors and to attracting new donors.

The new appropriation is distinct from the $90,000,000 (endowment) appropriation announced by The Ford Foundation in December, 1955, to help privately-supported medical schools stregthen their instruction.

Progress in Allergy

MISCELLANEOUS REVIEW OF ALLERGY—1955

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IN THE past, Forman[52] has collected nearly 20,000 references in the field of allergy and applied immunology. He advocates the use of workshops on medical writing as offered by The American College of Allergists in association with the American Medical Writers' Association. He reports that librarians say reviews are the most sought after class of literature in medical libraries. In his interesting article, Forman believes that each author should write a suitable abstract of his material, a practice which would add greatly to the efficiency with which the results of research are integrated into the body of knowledge. The review article, according to Forman, supplies background to both the researcher and the clinician on any phase of the particular subject in which the individual may be interested. Some of the reviews published in the ANNALS OF ALLERGY will have several hundred references from which to choose. In writing this miscellaneous review of allergy, the attempt has been made to be quite selective and to include those writings which would not ordinarily be covered by other reviewers.

ALLERGIC REACTIONS

The allergic reaction may assume many forms. Sherman[127] describes allergic reactions as being anaphylactic in type, as compared to the local vascular reactions, gradually progressing to necrosis of tissue commonly recognized as the Arthus reaction. Serum sickness is noted when sensitization results from a large injection of an antigen which persists in the body through the period of antibody formation. Atopy is described by this author as being a somewhat similar form of sensitization which is acquired through inhalation or ingestion of antigens. Manifestation of atopy on subsequent exposure to this antigen is noted with asthma, hay fever, perennial allergic rhinitis, angioedema, urticaria and certain gastrointestinal and cerebral reactions. Contact dermatitis and tuberculin allergy are other types of allergic reactions which illustrate the varieties but not all of the allergic phenomena. Anaphylaxis and the Arthus reaction are most readily produced by typical protein antigens. Contact dermatitis, produced by a variety of simple chemical compounds, is only rarely produced by protein antigens. The natural development of contact dermatitis depends upon the penetration of a sensitizing dose of the allergen through the unbroken skin. Shock organs show a greater degree of reactivity to contact with the antigen. The clinically important shock organ is simply the organ most exposed to the antigen by natural contact. The occurrence and intensity of allergic reactions in the intact organism may be influenced by a number of nonspecific irritations and infections. In anaphylactic sensitization, the injection of a sublethal dose of antigen reduces the susceptibility of the animal to shock by subsequent injections of the same

antigen. In respiratory type of allergy, such as hay fever or asthma due to inhaled allergens, good protection may be produced by a series of injections of gradually increasing doses of antigen. Control of these respiratory allergic diseases by antigen injections does not depend on exhausting the supply of antibody. The blocking antibody has not been conclusively proved to be the protective factor but it appears probable that the phenomenon is actually one of immunization rather than desensitization. In tuberculin allergy, true desensitization may be produced in experimental animals by injections of antigen, but the details of the mechanism of desensitization are unknown.

Clinical allergic reactions are not all dependent upon the same immunologic mechanism. Sullivan[136] believes the attending physician at the bedside should try to visualize as thoroughly as possible the pathology or the disturbed physiology of allergic reactions. He considers the two most outstanding features of allergic diseases to be the general characteristics of the clinical reaction and the time interval between challenge and development of the reaction. Sullivan states that some clinical diseases are always due to the same immunologic mechanism. Thus immediate shock following injection of an antigen is always due to plasma antibody acting immediately with its antigen to create a "histamine-like" or protease effect. Other clinical diseases such as asthma, allergic rhinitis and urticaria are not due to the same immunologic mechanism in every patient or even in the same patient every time. The mere demonstration of specific plasma antibody does not prove that plasma antibody is responsible for all observed reactions. The correct diagnosis, as the name of a disease, does not carry with it an identification of the immune mechanism. Ideally, however, management of the patient with an allergic reaction should require the diagnosis to be extended beyond the confines of the diagnoses listed in the standard nomenclature of disease. Ratner[113] considers allergy to be a battle against the invasion of foreign substances into the body through inhalation, ingestion or injection. He writes that the wheal is the final unit of allergic reaction, assuming that there is an extensive multiplication of this wheal-like mechanism involving visceral and systemic areas. Organs containing the largest amount of smooth muscle cells are those in which predominant manifestations of allergic diseases are present. The sudden constriction of an arteriole initiates the wheal formation, which development and progression applies to all allergic vascular reactions. A major role in allergy is the union of antigen and fixed cellular antibody resulting in cellular irritation. This produces physiologic disturbances of the affected tissues. The characteristics of this affected tissue determine the type of syndrome which develops. A thorough understanding of the basic mechanism of allergic phenomenon is possible only through the study of the various ways in which antigens invade the body and produce interactions with tissue-fixed antibodies.

PREVENTION AND POLICY

Preventive medicine is logically a part of general practice, but all doctors should aid in giving their patients the benefits of it. An editorial[42] states that the allergists have an unusual opportunity to practice preventive medicine since their patients must make periodic visits over long periods of time. No specific program is outlined in this editorial, but the allergist is reminded of the opportunity that awaits him. As part of the allergy investigative studies, we should open the door, so to speak, to reasonable

preventive medicine. In addition to the care and investigation for allergic diseases, the allergist is in an ideal position to warn his patient of danger and to see that he receives care from his family physician for any illness or corrective procedure that may be impending.

Prince[109] states that allergy has proved its place among the specialties. An independent board for certification of allergists is considered to be mandatory for recognition of this high level. Proficiency in either internal medicine, pediatrics, or both, should be a prerequisite to certification in allergy, according to this author. Formal certification would not make any allergist a better physician, but it would provide greater facilities for adequate fundamental training and study. Sheldon[126] believes that medical education is a subject of the utmost importance for the future of allergy. The instruction of the undergraduate medical student in allergic problems has lagged behind the organized presentation of other subjects in the field of medicine. Little time is devoted to the subject of allergy in most medical schools because there is a tendency for the instruction to be left up to several departments. This results in a disproportionate lack of emphasis in relationship to the clinical importance of allergic diseases. The actual curriculum of instruction for the undergraduate medical student should contain provision for a reasonable understanding of the immunologic aspects of allergy. There should also be concentration on the clinical entities which allergic diseases may produce. Prince[110] again emphasizes the importance of allergy as a specialty. He states that adequate specific allergy diagnosis and therapy require specialized intensive training and experience which cannot be acquired in any sort of sideline endeavor. The failure of allergy to attract more young physicians will lead to allergic patients being treated by physicians inadequately trained in this specialty, with emphasis only on symptomatic relief measures. There will be a disregard for specific manipulation unless this paradoxical situation is corrected.

POLIOMYELITIS

Lubens[90] has made a study of the incidence and severity of poliomyelitis in patients with an allergic history. In epidemics during 1949 and 1950, the incidence of poliomyelitis was approximately the same in allergic and nonallergic individuals. The incidence of bulbar cases, however, was 2.4 times as great in the 1949 epidemic and five times as great in the 1950 epidemic in the group with allergic histories as in the group without them. In each of the two studies Lubens found the number of poliomyelitis patients who proved to have a major allergic history was approximately equal to the number without such a history. In those cases with a major allergic history, the mortality was greater than those without such a history. His findings would seem to warrant a similar study on a large scale by allergists in various parts of the country in order to determine if the allergic constitution is related to the severity of poliomyelitis. His results indicate that such might be the case. In an editorial,[41] attention is called to a group of treated allergic patients in which only the anticipated rate of poliomyelitis was encountered. Immediate consideration by the national allergy societies should be given to the preliminary data that has been published. It is imperative that allergic individuals be given the proper immunologic therapy in areas where poliomyelitis occurs. There is a marked need for suitable immunologic, pharmacologic and physiologic control of the neurovascular system that responds by allergic inflammation.

Holbert[70] interviewed by questionnaire 100 patients with severe residual signs of poliomyelitis. Sixty-two per cent of these 100 patients had one or more allergic diseases in their pre-polio history. The most frequently encountered allergic disease in these patients was urticaria, which had been present in 34 per cent. Thirty-one per cent of the total number questioned had major allergic conditions. When this is compared to a 10 per cent incidence of major allergic illness in the general population, these figures become more important. This author believes that there must be some factor which would explain the apparent higher incidence of allergy in polio patients, and questions whether the allergic state favors systemic invasion by the polio virus.

ALLERGY IN CHILDREN

Under proper circumstances, adequate allergic therapy includes correction and removal of associated pathology, avoidance of any suspected causative agents, medication directed toward symptomatic relief, a period of hyposensitization and, finally, psychotherapy if indicated. Criep[32] expresses his opinions in discussing the outlook for the treated allergic patient. He believes that the patient suffering with nasal, bronchial or skin allergy has an excellent chance of either complete recovery or of keeping his condition well under control. The provision is made that the diagnosis should be accurate and treatment should be started early. Failure to provide adequate allergic treatment for a large group of allergic patients frequently has disastrous effects. Proper allergic therapy should be instituted early.

Collins-Williams and Ratner[30] very adequately covered the subject of pediatric allergy, reviewing ninety-seven published references in this work. Kohn,[82] on the other hand, reviewed the subject of physical allergy from thirty-five references. Pediatric allergy was reported much more frequently than were conditions involved in physical sensitivity.

The significance of eosinophilia in children is not entirely understood and is often unexplainable. Stafford[130] reviewed all of the differential blood counts done in his private practice with special attention to the percentage of eosinophils found. Of 1,107 counts performed, the average percentage of eosinophils was 4.02. The highest percentage found was 43 per cent in a case of Loeffler's syndrome. Though eosinophilia is characteristic of allergic reactions, its relation to hypersensitization is not known. If the eosinophilia is otherwise unexplained, Stafford thinks that suspicion should be aroused that the patient is suffering from some form of allergy. The mere existence of eosinophilia, however, does not make a definite diagnosis unless the history is positive for allergic disease and findings are suggestive of these conditions. Eosinophilia can appear sporadically in children who are otherwise entirely well. Kaufman[80] has highlighted certain aspects of allergy, particularly as they apply to infants and children, and states that the prevention of allergy may actually begin during intra-uterine life. Preventive allergy is all important; and even though the prophylactic phase of allergy has been neglected or disregarded, the potentially allergic infant can be protected. Dietary control is an all-important bulwark against development of allergic disease. As an example, it is stated that boiling the milk renders it less allergic and acidification enhances its digestibility. Kaufmann offers the opinion that feedings should be introduced in small quantities at the beginning and increased as needed. Environmental control is stressed by this author as an important

consideration in antiallergic programs. Though hypersensitivity phenomena in the pediatric age group are essentially and basically the same as those which occur in the adult, the responses of infants and children to all allergenic stimuli often are manifested differently. Kaufmann says that the benefits obtained from appropriate allergic management are indisputable and to neglect or ignore this fact is lamentable.

Emotional problems may have an effect upon the disease symptoms of allergic children. Shivers[128] has noted the similarity in personality types in the family group of an allergic child. He has noted that the mothers of allergic children are often serious and consider the bringing up of their children as serious business. These mothers usually are overprotective and exhibit concern over all of the details of the child and his environment. Thus, allergic children tend to be on the shy side, clinging to their mothers, lacking self-confidence and often mixing rather poorly with other children. Successful treatment of the allergic child includes the consideration given to emotional problems to be on an equal level with the more routine investigative measures and specific or nonspecific treatment. Dees[34] finds that physicians and parents are becoming increasingly aware of allergy as a cause of respiratory and other symptoms in children. The best demonstration of this is the decreasing age in which patients are being seen in the allergist's office. However, an allergic basis for so-called "colds" is not recognized. No matter how young the patient, if wheezing is present, asthma should be considered as the most likely cause, particularly, according to Dees, if the pediatrician's previous knowledge of the child includes bouts of feeding difficulties that have been clearly relieved by dietary changes. Frequent colds without much fever and with these controlled by antihistaminic preparations are important indications that asthma may be present regardless of the age of the patient. If the first symptoms of the original asthmatic attack stand out with clarity in the mother's memory, one may be able to identify a causative allergen. On the other hand, if the first attack cannot be clearly recalled or the trouble began insidiously, the physician is apt to be dealing with infection of some nature or with sensitivity of a less violent type. It is wise to remember that the younger the child the more quickly he will become dehydrated during respiratory distress and the more important is his need for fluid.

A controversial subject of great importance is the use of antibiotics in allergic children. Most pediatricians will state that allergic children do better when given antibiotics as early as possible after the onset of infection. If there is no improvement after twelve to eighteen hours of purely antiallergic measures. Dees treats the asthmatic child with antibiotics. The most important part of a pediatric or any allergy program is the rapport between doctor, parents and patient. Dees considers this to be an invaluable asset in the hands of every physician who has the primary care of the allergic child.

SKIN TESTS

Skin testing with allergenic extracts is a valuable diagnostic procedure, the appreciation of which may be lost through its injudicious use. Peshkin[107] emphasizes the need for standardization of allergens. He also focuses attention upon the disadvantages in using test solutions containing a group of related allergens. A positive skin test reaction indicates sensitization that may have been present either in the past or it may

indicate a potential factor of allergy. An individual may have active clinical symptoms but testing will produce negative reactions even though the causative substances are determined by other means of identification. For example, an offending food may be determined by a test diet when skin tests with food extracts are negative. The size or intensity of a positive reaction to an allergen does not determine its importance in the etiology. For the inexperienced investigator the method of choice for testing, especially in children, is the scratch test, because of the safety factor involved in this method. Those individuals who fail to react to skin testing but who possess clinical symptoms, and are eventually treated with pollen or other inhalant extracts, will invariably fail to be relieved of their symptoms unless the dosage of those extracts is carried at a very high level. Larger doses of specific allergenic extracts is the final goal of treatment for protection of the patients who do not show positive skin test reactions.

The limited value of skin testing with food allergens is the subject of a very interesting editorial.[43] Even in a person with a known clinical sensitivity to an antigen, the skin test may be negative. Skin tests, therefore, are of diagnostic value only if interpreted in the light of clinical findings. False positive tests due to contamination of a syringe or a test solution with an allergen other than that being tested are probably more frequent than is generally realized. It has been pointed out that positive skin tests to inhalants rarely become negative, whereas positive skin tests for food may become negative with avoidance of the food causing the clinical symptoms. In this same regard, Tuft and his associates[141] reveal the incidence of positive skin reactions to food allergens to be highest in the first decade of life. There is a slight decrease up to the age of fifty, after fifty and especially after sixty a sharp decrease in the incidence of positive skin reactions to food allergens has been noted. This failure to demonstrate positive skin reactions in older persons may be due to loss in skin reactivity rather than to a lack of specific hypersensitivity. As a result of this variation, some persons often are classified as being nonsensitive or nonallergic. Their studies suggest that failure to react may be corrected when a stronger extract is used for testing. Since most people react to histamine in a 1:10,000 or a 1:100,000 concentration, routine skin tests with these concentrations might provide a clue to the patient's skin reactivity. Tuft, Heck and Gregory utilize this method of testing for an estimation of their patient's skin reactivity. Regardless of which concentration is utilized, they demonstrate graphically that in nonallergic persons the reactivity of the skin in relation to histamine is highest in the first decade.

Tuft and Heck[142] also have shown that allergenic contact is extremely important in the induction of sensitization. This is more noticeable in atopic persons than in normal persons. Excessive antigen contact may convert a nonclinical sensitization into a clinical one. Children with positive tests to commonly eaten foods are found to use these foods in large amounts. These patients should be warned to be more conservative in the ingestion of the foods for which positive reactions are shown. The allergist is usually more concerned with determining the clinical or nonclinical nature of a positive skin test reaction than with attempts to determine the manner in which the sensitization developed. These investigators have worked with horse serum in sensitive and nonsensitive patients, revealing that some individuals sensitive to horse epithelium often are sensitive to horse serum because of the presence of a common antigen.

This is not always true. Some individuals may be sensitive to horse epithelium alone and, on occasion, may be given horse serum injection without a resultant reaction. Extreme care, however, should be used in the administration of this preparation to these individuals. Of the seventy patients tested by Tuft and Heck showing positive skin reactions to horse serum, forty-seven were positive to horse serum alone and twenty-three to both horse serum and horse epithelium. Of the entire group of seventy patients with positive reactions to horse serum, only seven patients with concomitant negative tests to horse epithelium failed to give a history of previous horse serum injection. They indicate that previous contact as a primary factor in the production of sensitization is all important. If this is true for horse serum sensitivity, it should also apply to sensitization provoked by food and pollen allergens. Both the type and duration of allergenic contact are important factors in the acquisition of sensitization to foods, so that the greater extent of contact the more likely that sensitization will result.

Impurities can be discarded as possible causes of sensitization by natural vegetable oils, according to Essellier and his associates.[49] The allergen here is either a constituent of the fatty oil by itself or a lipoid with very similar physical or chemical properties, which was not separated from the glycerides during the refining procedure. They performed sensitization experiments with chemically pure butyric acid, tributyrin, tripalmitin and triolein. Repeated injections of triolein may produce sensitization. This preparation is slowly absorbed and may remain in the skin for several weeks. Because of this slow absorption, cutaneous signs do not disappear after a few days, as with tuberculin, but may last for several weeks. They suggest the triolein may behave as a hapten, and consider it significant that it is the triglyceride of an unsaturated acid. The oleic acid is the sensitizing agent and not the glyceride of the saturated palmitic and butyric acids. Such sensitization is not accompanied by a rise of the blood eosinophils. This, however, does not speak against the allergic nature of these reactions.

Do positive tests for bacterial allergy have a diagnostic significance with respiratory allergic disease, angioedema, rheumatic fever, rheumatoid arthritis and many conditions of the eye and ear? Blatt[13] has thoroughly investigated this problem, and his answer is definitely in the affirmative. The test which he and his co-workers have devised would reveal that bacterial allergy not only plays an important part in certain persons with allergic manifestations but is, in some of them, the primary cause. Though bacterial allergy is one of the most important it is, unfortunately, one of the least explored aspects of medicine. There is, however, no generally accepted treatment for bacterial allergy, and most physicians are content to use only symptomatic therapy. Chemotherapy and the use of antibiotics have given much support to this latter feeling. A controversial subject is the use of bacterial vaccines and filtrates; the controversy, however, is not concerned with their value but is involved with the manner of their action. Blatt feels that the use of bacterial vaccines and filtrates can be upon a sound immunologic basis. Baird[7] disagrees, stating that the immunizing effect of bacterial vaccine is truly nonspecific. There is not adequate proof of specificity of reaction of the body to all strains of bacteria, according to this author. He therefore considers autogenous vaccines to be unnecessary since the original bacterial strains are altered by the processes of culturing and attenuation. Accurate standardization of commercially prepared stock vaccines is one point in favor of using the nonautogenous type.

Strauss and Spain[134] describe a new micro Seitz type filter. This new filter consists of a lower section, to one outer end of which is attached a hypodermic needle. The inside of this section has a funnel-like appearance on which is placed a washer and a wire screen supporting a 10 mm Seitz filter pad. This center section has a capacity of 10 ml. For sterilization, this small unit is attached to a vial with a rubber puncture cap. There is another small hypodermic needle stuck into the rubber cap to release any positive pressure. A pressure of 10 pounds per square inch has been ample in any filtration. It would seem to be very practical for the sterilization of small amounts of material.

Kaplan[79] exposed mats of fungi to sonic vibrations in order to avoid drying and grinding procedures in the preparation of extraction. The action of sonic vibrations on molds is shown to be the same as on bacteria. Sonic vibrations in the range of 9000 cps have little or no denaturation effects on the chemical identity of the cell material of microorganisms. He therefore prepared mold extracts according to this method. The fungus mats were suspended in normal saline, and these suspensions were introduced into the transducer cup of the magnetostrictor and subjected to sonic vibrations of 9000 cps for a period of thirty minutes. Most cells were ruptured after this period of time. Twenty-five per cent of his patients gave positive reactions to one or more species of *alternaria* and related genera. It was hoped that the results of Kaplan's study would point to a higher specificity of the experimental extracts as compared to the standard extract with which comparison was made. The use of sonic energy to liberate the allergen from the fungus during preparation of the extracts would appear to yield a more specific preparation than by other standardized methods of preparation. Kaplan stated that his extracts appeared to be potent, specific and nonirritative. He could determine no common excitant in all species of *alternaria*.

It is only recently that the importance of fungal spores as sensitizers has been intensely investigated. Maunsell[97] states that the best method of investigating fungal spores is to identify the spores and count the number by means of suction traps. She was able to determine the dominant fungus in London to be *penicillium*. *Cladosporium* reached very high concentrations during the months from June to September. Fungi were most prevalent in humid areas with indoor fungal clouds being very high in damp buildings. Dock workers, second-hand furniture dealers and gardeners are among the large number of occupations which meet the hazards of sensitization by fungal spores.

COLLAGEN AND ALLERGY

O'Brien[102] has used the term "collagen diseases" to refer to a group of conditions that are characterized by widespread involvement of collagen and ground substance. No specific connotation is applied to the term collagen. Pathologic alterations of collagen are noted in such diseases as serum sickness, asthma, rheumatoid arthritis and rheumatic fever. The etiology of collagen diseases, however, remains obscure. The causative factors receiving the greatest consideration are sensitivity to an antigen, infection, endocrine abnormality and vasomotor disturbances. That the basic factor of collagen diseases is an antigen-antibody reaction has been pointed out by other investigators. O'Brien quotes Rich and his coworkers as having determined that drugs are frequently associated with, if not related to, the development of periarteritis nodosa. Because the cardiovascular system is rich in collagen material, widespread damage occurs

through cardiovascular structures and associated organs. Inflammation, degeneration and fibroblastic proliferation characterize the pathologic processes of collagen diseases. The character and individuality of each collagen disease is due to the variability of distribution and character of these pathologic processes. Some degree of anemia can be encountered in all of the collagen diseases, being most severe in disseminated lupus erythematosus and in periarteritis nodosa. All of these collagen diseases are at times associated with a reversal of the normal albumin-globulin ratio. Biopsy studies are important in order that a diagnosis may be definitely established. It may be necessary to subject more than one area to biopsy before the diagnosis is definitely established. The treatment of collagen diseases is largely symptomatic, and O'Brien acknowledges that effective steroid therapy has not materialized as the answer to these problems.

Of all of the drugs prescribed in the therapy of scleroderma, for example, para-amino-benzoic acid has been the most effective. Results obtained by the use of vitamin E are relatively insignificant. Talbott[139] asserts that supportive measures in the treatment of collagen diseases are the only means available. High on this list are the steroids—ACTH, cortisone, hydrocortisone or prednisone. In the diffuse collagen diseases, significant alterations occur in cellular structure as well as in the ground substance. In fibronoid degeneration there is an increase in the number of fibroblasts and an increase in intercellular substance. Some of these changes may be proliferative reactions and others may be degenerative changes. The collagen may become granular and the ground substance visible. Infiltration with leukocytes completes the picture with inflammation, proliferation and degeneration being the main characteristics of collagen diseases.

The four maladies generally considered to be in this group are polyarteritis, acute dermatomyositis, generalized scleroderma and acute disseminated lupus erythematosus. Polyarteritis is the only dyscrasia in the group of collagen disorders that has permitted any clue regarding etiology. The internal lesions may be manifestations of hypersensitivity, as above mentioned, being due to various types of drugs. The vascular lesions of periarteritis may be due to the antigenicity of a variety of drugs, such as sulfonamides, Dilantin,® mercurial diuretics, thiouracil, penicillin, arsenicals, iodine, cortisone and ACTH. Outstanding in all of these collagen diseases is the spread of the involved areas. Periarteritis nodosa has been recognized since the late nineteenth century. The morphology of this disease is characterized by eosinophilic leukocytes invading and by fibronoid necrosis destroying the walls of the blood vessels.

Szymanski[138] classifies necrotizing vasculitis as being in four entities: (1) cutaneous allergic vasculitis; (2) systemic allergic vasculitis; (3) granulomatous allergic vasculitis; and (4) periarteritis nodosa. He describes each of these conditions in detail. He considers allergic vasculitis and periarteritis nodosa to be distinct diseases, reserving the latter term for systemic diseases of necrotizing vasculitis in which clinical evidence of sensitization is absent. Sensitivity to serums and drugs seems to be the most important etiologic mechanism noted in the cases of systemic allergic vasculitis. This is a fulminating disease of short duration, the terminal illness extending from a few days to a few weeks but always less than one month. Widespread involvement may be observed. There seems to be a distinct site of predilection which distinguishes systemic allergic vasculitis from periarteritis nodosa in the opinion of this author. In systemic allergic vasculitis, lesions are present in the pulmonary vessels and in the follicular arteries of the spleen, which are not found in periarteritis nodosa.

Though myocardial lesions have been described, eosinophilia is a raritv. Since ACTH or cortisone may be life saving, a rapid diagnosis is imperative. Confirmation of such a diagnosis is made by a skin or kidney biopsy. As a part of a generalized penicillin reaction, the patient of McGinn, Ricca and Currin[91] developed a generalized arteritis as diagnosed by biopsy. A final diagnosis of Kaposi's sarcoma was made from the appearance of the arteritis changing during subsequent biopsies. This low-grade malignancy has been reported following other conditions such as lymphatic leukemia, Hodgkin's disease and hemolytic anemia, but the authors consider this to be the first reported occurrence of Kaposi's sarcoma following allergic angiitis.

TREATMENT PROBLEMS

Maietta[93] presents the therapeutic problems of sixteen allergic female patients who have been treated for allergic rhinitis, hay fever and bronchial asthma during their pregnancies. It is important for the allergists to remember that constitutional reactions following pollen desensitizing injections may appear with dramatic suddenness and may involve the uterus. Such involvement of the pregnant uterus as a shock organ has led to abortion. For this reason if for no other, the author recommends that extreme caution be exercised in the management of the pregnant patient. He believes in conservative therapy because of the danger of a constitutional reaction. Each pregnant patient should be considered separately with the antiallergic treatment being individualized to fit the needs of the patient. He recommends the use of diminutive pollen doses combined with an antihistaminic preparation. Cheerful assurance that the presence of allergic symptoms will not necessarily disrupt the pregnancy nor will the pregnancy aggravate the allergic picture is part of the psychotherapy that must be employed with these patients.

Clark[25] has employed sodium bicarbonate and potassium bicarbonate in various proportions and amounts in patients with acute chronic allergic manifestations. He administers 5 grams of the combined alkalis dissolved in water every hour or two for one, two or three doses. Consistently good results are reported by this author, particularly in acute cases of allergy. Chronic allergic diseases, such as severe and persistent bronchial asthma do not receive benefit by this method of alkali therapy, and its use is reserved primarily for acute allergic shock. For example, in anaphylactic shock due to penicillin, the recovery is rapid and complete. Improvement is noted in from seventeen seconds to a minute or two. Since time is a very important factor in acute allergic shock, the intravenous administration of alkalis is recommended by Clark. During major surgery, a lactate solution may be preferable to sodium bicarbonate since the desired action is more prolonged and less prompt. Caution, however, should be exercised when cardiorenal, hypertensive and arteriosclerotic diseases are present.

Harris[66] has found numerous allusions to the emotional component in allergy disease upon reviewing the literature. Psychosomatic medicine appears to be on the filmy fringe of allergy and one must realize, according to Harris, that many patients tend to dramatize their symptoms and emphasize the emotional upsets. He suggests that we not condemn the patient who seeks to validate his nonmedical diagnosis of the etiology of allergic disease as one of emotional or psychosomatic origin. It must also be remembered that exact and definitive etiology of allergic disease is frequently obscure. Whenever etiology is unknown or difficult to determine,

the illness is frequently classified as due to nervous influence. He concedes, however, that there is no separation between psyche, the mind, and soma, the body; and that psychosomatic influences aggravate and, in some cases, precipitate a *rare* allergic reaction. Asthma may occur as the accumulation of an anxiety, as an emotional conflict, as a means of escape and as a conditioned response. All psychologists do not agree that maternal rejection is the specific emotional factor causing bronchial asthma in children. Psychotherapy is a valuable adjunct in allergic therapy, but it should not be used as a curative measure to the neglect of the actual etiologic factor which is organic. The allergist needs the psychologist and his therapeutic approach as an assistant. Harris maintains that, in this way, the specialty of allergy marches with time and keeps pace with medical progress in all its branches.

ALLERGY AND THE EYE

A large percentage of ocular diseases is associated with allergic manifestations. The allergic conditions described and discussed in detail by Donegan[38] affect the eyelids, conjunctiva, cornea, sclera, uveal tract, lens, cubic nerve and retina. Superimposed bacterial infection is quite common in allergic conjunctivitis. Donegan describes vernal catarrh as being a special and interesting form of conjunctivitis which is often cited as the classic allergic disease of the eye, and is so named because of its seasonal incidence. Treatment, however, has usually been unsatisfactory, although there is satisfactory response to hormonal therapy. Since the conjunctiva protects the sclera, the only allergens affecting the sclera are those in the circulation. Diffuse and localized episcleritis with deeper involvement resulting in scleritis are principally expressions of allergy to tuberculoprotein. Atopic cataract may be associated with allergy of the skin. Donegan comments that intra-ocular inflammation (known as phacoanaphylactic endophthalmitis) following traumatic, surgical or spontaneous rupture of the lens capsule is due to allergy to lens substance.

Epstein[48] found several reports in the literature of cataracts occurring in patients with atopic dermatitis who had never had x-ray therapy. Most dermatologists believe that these cataracts are related to the atopic dermatitis and not to the x-ray therapy some of these patients may have received. Brown[19] could recall only two cases of bilateral cataract associated with atopic dermatitis. Cazort[24] states that he originally reported a case of bilateral cataracts in a child who had never had any radiation therapy. These reports have been noted in answer to questions concerning the association between cataracts in atopic dermatitis in patients who had received radiation therapy. Waldbott[146] reviewed 20,000 patients over a period of the past thirty years and found twelve cases of cataracts in conjunction with infantile eczema. He warrants that he had never seen cataracts as a part of contact dermatitis. This same author, in a symposium on ocular allergy,[137] notes that atopic dermatitis in early childhood is primarily caused by foods and later may be evoked by pollens, fungi and house dust. Dermatitis around the eye may be an atopic response to inhaled or ingested antigens or a contact lesion caused by external agents. Conjunctivitis may occur as part of vernal catarrh, hay fever, chronic nasal allergy or as part of an acute reaction termed allergic shock. Glaucoma may be associated with chronic serum sickness, food allergy or systemic reactions to sulfonamides. When the ciliary vessels act as a shock organ, ocular tension is thought to be increased. In this same symposium[137]

Hansel states that dermatitis of the lids, blepharitis, vernal conjunctivitis and keratitis are usually caused by contact agents. The ever-increasing local application of drugs and the universal use of cosmetics by women are thought to be responsible for contact allergy's being the most frequent and important type of ocular allergy encountered. Theodore[137] asserts that two other common forms of eczema of the eyelids must be differentiated from contact allergy. The first of these is the infectious eczematoid staphlococcal dermatitis of the eyelids, the second a nonspecific eczema of the eyelids which develops under certain generalized conditions such as atopic dermatitis, neurodermatitis or seborrheic dermatitis.

Prewitt[108] regards emotions as playing a large part in glaucoma, in which they may be the dominating factor in specific cases with a resultant detachment of the retina. A case of retinal detachment reported by this author suggests that stress and/or allergy may produce the same pathologic picture as infection, trauma, metabolic disturbances, blood dyscrasias and atherosclerosis. This same procedure may explain some of the so-called idiopathic disease noted in the past. He feels that psychic trauma in a susceptible individual may produce a profound change in the eye parallel to organic changes.

A clinical study of almost 2,000 cases of vernal conjunctivitis has been reported by Alimuddin.[3] These 1871 instances represented about one-third of the ophthalmologic cases seen by this author during the summer months in West Pakistan. Palpebral, limbal, and irritative types comprise the three clinical expressions of this disease. Conjunctival scrapings always showed three to five eosinophils per field. The most commonly associated allergic conditions were urticaria, angioedema, contact dermatitis or eczema. There was some conversion from the irritative type into the libal type over a three-year period, but there was no conversion to the palpebral type.

BEDBUG REACTION

Parsons[105] reports a case of sensitivity to bedbug bites eleven years after the patient was originally exposed. Following the bite, the individual awakened with choking, his arm swollen to twice its normal size and in a state of general collapse. Seven minutes after a later test bite, marked local reaction was present at the bite area. Fourteen minutes after the bite, a noticeable drop in blood pressure was observed. Epinephrine returned the blood pressure and pulse to normal, and the generalized itching and pallor, which had been present, disappeared. The original shock symptoms noted with the bite of the bedbug had been misinterpreted as coronary occlusion.

INHALANT ALLERGY

Some of the remarkable features of similarity and dissimilarity between industrial and domestic factors of inhalant allergy were pointed out by Halpin.[63] Inhalant allergy may be identical regardless of geographical location, but the ultimate agents of cause will be dependent upon the type of industry found in that particular area. This author cities three instances in which domestic and industrial components of inhalant allergy appear to be in union with or in open opposition to the production of asthmatic complaints. The importance of industrial allergy is marked in that community whose livelihood is closely associated with potential sources of trouble. Emphasis is added to this statement in that the patients who live in the

Middle West, which is primarily an agricultural community, present symptoms primarily based on grain or mold sensitivitv. It is pointed out that some farmers are unable to work in their harvest field, that some cattle feeders cannot work in close association with their stock or their feed, and some mill workers are unable to continue in their occupation because of the industrial "hazards." Modern industry is acutely aware of the necessity of dust control, particularly in the grain-milling business. Halpin describes in detail the methods used for dust control and elimination in a large cereal plant in the Middle West.

NASAL ALLERGY

All children with nasal symptoms should have a thorough nose and throat examination. Differentiating allergy from infection is essential in all nasal cases, and Sanders[122] demands that a thorough nasal examination be performed before the removal of tonsils or adenoids. He discourages the routine use of antihistamines and antimicrobials without a diagnosis. There may be many variations in the appearance of the nasal mucous membrane, though the usual allergic appearance is supposed to be pale, glistening and edematous. Uniform density in all sinuses is the rule if there is involvement of these areas. Sanders does not consider surgical procedures on the sinuses to be satisfactory; one operation does not necessarily call for another. Surgery is done primarily to establish drainage or remove diseased tissue. Jones[77] asserts that otorhinolaryngologists practicing allergy and the general allergists have many mutual problems. In his practice, perennial allergic rhinitis is the most important and the most common allergic finding from the nose and throat standpoint. Diagnostic tests are considered justified only when the history is classic and a complete physical examination with laboratory studies is in agreement with the diagnosis. Every patient with upper respiratory symptoms should receive the benefit of a thorough otolaryngologic examination. He discusses a typical case report, presenting evidence of serous otitis upon an allergic basis in which the etiology was not obvious and the response to treatment had not been good. Allergy management was successful in relieving the patient's complaints.

There are many patients in whom sinus surgery will not provide good results. Sanders[123] notes that the allergist will see more of these patients than any other physician because if a patient had obtained good results from surgery he would not seek help from the allergist. Sanders comments that the otorhinolaryngologist may have overdone the teaching of conservatism, and he feels that there has been established a fear of sinus surgery, based upon the failure of the physician to recognize the definite indications for these surgical procedures. He decries the traumatization bv surgery or local medication in the acute allergic nose. In the presence of acute infection, drainage procedures may be indicated, but the intermittent nasal obstruction of allergic origin should be controlled by management of the basic allergy. Nasal polyps of allergic origin usually appear on the roof of the nose. Some of these small polvps may recede under proper management of the allergy, and they should be given the opportunity to do so, but as the tissue changes become less reversible and the polyp increases in size, surgical removal should then be accomplished. Nasal polyps from the floor of the ethmoid sinus between the middle turbinate and the lateral wall of the nose are usually caused by infection in the ethmoid cells. In the absence of any polyps on the roof of the nose, suspicion

should be that superimposed infection is the probable cause. Sanders observes that hyperplastic sinusitis is very easily confused with allergic sinusitis, as polyps may be present with either disorder and there is usually a uniform thickening of the sinus mucosa even without purulent discharge. Uniform enlargement of some, but not all, of the sinuses by x-ray should make one suspicious of a hyperplastic sinusitis. Because of dependent drainage, the frontal sinuses seem to have more recuperative power than other sinuses. If the frontal sinuses do not clear under proper management, there may be clinical evidence of disease around the frontal ostium. The secret of success in treating frontal sinusitis is removal of every vestige of the frontal mucosa, including any infected ethmoid cells, or correction of any high anterior deviation of the septum.

SEASONAL DUST SENSITIVITY

Sustained residence within a certain range of temperature may serve to favor the onset of aggravation of respiratory symptoms due to house dust sensitivity. Targow[140] indicates that increased exposure to house dust in cold weather may be less important in causing asthma in some individuals than the lowered temperatures to which they are subjected at this time. Even then, temperature may not always be the factor involved. Relative humidity may be the precipitating factor in some instances, while other patients may require a combination of temperature and humidity changes. The initiation or aggravation of complaints may result from such combinations as the annual cycles of changes in mean temperature, relative humidity or barometric pressures. There are certain patients who are sensitive to house dust in whom symptoms are initiated or aggravated in warm weather rather than in cold weather. It can be understood how difficulties could be created in both the diagnosis and management in this distinctive clinical form of house dust allergy. If the patient should show marked positive reactions to one or more of the seasonal inhalant allergens in addition to house dust, the diagnosis of what might be termed "warm weather" house dust sensitivity may be overlooked. Targo writes that if the patient with seasonal symptomatology during warm weather fails to respond to specific therapy with factors other than house dust extract, the physician should begin to question the possibility of a complicating overlooked house dust sensitivity. It must be kept in mind that clinical house dust sensitivity may account for allergic symptoms regardless of the time of the year that the symptoms may occur. Targo advances the hypothesis that symptoms are provoked much more readily in some individuals when they become exposed to a certain range or zone of values. This range or zone may be different for different individuals.

A case of spontaneous cerebral spinal rhinorrhea simulating allergic rhinitis is reported by Berryman.[12] It is the problem of the allergist to determine the cause for rhinorrhea when it is the presenting complaint of the patient. It is frequently necessary to eliminate simple vasomotor instability and infection which may simulate or obscure allergic conditions. Though the condition of cerebral spinal rhinorrhea is admittedly quite rare, it can produce "rhinitis." This author reports a case of cerebral spinal rhinorrhea, a condition which may result from trauma, neoplasm, congenital anomaly or spontaneous presence. In this particular patient the likelihood of a defect in the cribriform plate permitting the escape of cerebral spinal fluid was confirmed when surgical closure terminated the patient's complaints.

Nasal allergy is responsible for most of the complaints in the practice of rhinology and also accounts for a considerable segment in the practice of the general allergist. Derlacki[35] states that the pathology of allergic rhinitis may be termed allergic inflammation of respiratory mucosa. Findings are characteristic of this condition in contrast to inflammation due to acute or chronic infection. The history, the appearance of the nasal mucosa, and the cytologic examination of the nasal secretions give presumptive evidence of an allergic cause of chronic rhinitis. Final proof, however, remains in the response to the therapeutic tests. If removal of a specific substance or treatment with an extract of this substance relieves the symptoms, and if the symptoms recur on re-exposure or with the discontinuation of treatment, it may be assumed that that particular substance is responsible for the symptoms. Food sensitization tends to produce a more continuous type of nasal obstruction with copious mucoid discharge than is caused by inhalants such as house dust sensitivity. Recently, however, Derlacki has changed his opinion regarding the foregoing statement. Food sensitivity now, in his belief, may produce intermittent nasal symptoms of a duration from several hours to several days with relative freedom from symptoms between frequent attacks. An uncomplicated food sensitivity is suggested by a relatively constant pattern of nasal symptoms uninfluenced by seasonal or environmental changes. He has found skin testing in food diagnosis to be practically without value. A food dairy and symptoms record are most inefficient in the establishment of a specific causative diagnosis of a frequently ingested food; instead he has employed individual feeding tests combined with the basic elimination diet and the individual food testing techniques. He advises his patient to follow a basic diet for about four days in order to unmask the possibility of any "masked" food sensitivities. On the fifth day, the first of the individual food tests may be given. If no symptoms are produced by this feeding, a second food test is given on the following day. If any of the feedings produce acute nasal allergic symptoms, there must be a forty-eight hour wait for the acute phase to subside before adding a new feeding test. It is only through a demonstration of cause and effect to the patient that the sound basis for subsequent dietary omission and subsequent relief of nasal symptoms is established. It then has been determined that the causative factors of the patient's nasal complaints are in his diet.

EPILEPSY AND HAY FEVER

Cohen and Janjigian[26] report an epileptic patient in whom they felt allergy may have had some etiologic significance. Their patient had symptoms of a seasonal nasal allergy; and with measures taken to relieve the acute symptoms, the electroencephalographic record changed to a normal pattern after having been abnormal. In this patient the first symptoms of epileptic seizures developed simultaneously with the first onset of symptoms of seasonal allergic rhinitis due to ragweed pollen sensitivity. The epileptic attacks were more frequent and severe during the ragweed season and were relatively infrequent in their occurrence during the remainder of the year. Dilantin® sodium did not control the epileptic symptoms, whereas an antihistaminic preparation was a most effective control.

In some instances attention to the psychic element in chronic vasomotor rhinitis will make this condition more responsive to treatment. Haiman[61] first uses a detailed history and thorough examination to precede an unhurried sympathetic questioning to learn as much as possible about the

pattern, followed by reassurance that the patient can get relief from his symptoms. The author feels that it is necessary to provide some relief of the most distressing symptoms at the time of the original visit. Local measures used in the nose consisted of ionization, vasoconstrictors or coagulation of the swollen turbinates. This "mind and body" approach is vital to the practice of medicine and is particularly applicable to those patients with rhinitis, sinusitis and nasal polyps.

METEOROLOGY AND HAY FEVER

Since it is the atmosphere which carries the allergens to the hay fever patient, meteorology is of primary importance in the problem of hay fever. Dingle[37] points out that there are certain weather events which are known to produce high pollen counts, and certain weather sequences which tend to produce an extended cumulative effect. He propounds that the seed bed, growth conditions in the spring and early summer, climatic data and long range forecasts for late summer can be "foreshadowed." The date of the beginning of the ragweed season, the antigenicity, and the amount of pollen can be predicted. Phenologic observations on the plants and the accumulative weather effects may be applied to correct the initial estimates. Thus one can adjust and improve the prediction as to the severity of the coming season. With these methods a high accuracy of prediction can be provided at least two weeks before pollen release begins. He believes there are several advantages to predicted pollen counts over the standard gravity slide counts, the chief of these being the availability of the prediction at least thirty-six to forty-eight hours before the gravity slides could be counted. In addition, the prediction would be more representative of the atmosphere overlying a whole city than would the pollen count taken at any particular place. The prediction would include estimates of the time variation of pollen concentration throughout the forecast period. Dingle says that there should be a co-ordinated attack upon the problem of seasonal hay fever by meteorologic, botanical, clinical and immunochemical specialists.

DYSPNEA AND EMPHYSEMA

There are many mechanisms involved in dyspnea, including apprehension, pain, mechanical hindrance to respiratory movements, intrinsic disturbances of the pulmonary apparatus and disturbances of the biochemical or reflex factors which control respiration. Ellis[47] has defined dyspnea as consciousness of difficult or distressful breathing. In this report the allergist will be interested chiefly in that part of the study which deals with obstructive diseases in emphysema or in asthma. Here the dynamic ventilatory tests are of special value with the prolonged expiratory phase indicating the type of dyspnea present. The maximum breathing capacity and timed vital capacities become progressively reduced with successive tests in these individual patients. This author recognizes that the clinical evaluation of dyspnea is often a simple procedure and that most of the tests to determine the type or degree of dyspnea are easily performed. Good information regarding ventilatory function may be obtained from the vital capacity, according to Ebert.[40] Additional information is found by observing the patient when he expires forcibly in performing the vital capacity test. Of even greater value is the measurement of the one second vital capacity or maximum breathing capacity. It is important to have a knowledge of the exchange of gases between the blood and lungs in

evaluating the function of the lungs. There is a general impairment of alveolar ventilation, and the carbon dioxide tension of the blood is increased during the late stages of pulmonary emphysema. Thus there results an increase in the total carbon dioxide content of the blood and in the carbon dioxide combining capacity. One of the simplest means of evaluating pulmonary function is to determine the degree of exercise required to produce any form of dyspnea in the patient. Pulmonary emphysema impairs alveolar ventilation because of over-all loss of ventilatory function and also because the air is not evenly distributed to the various alveoli.

The bronchi in the bronchiectasic lung are usually macroscopically dilated. Beattie[9] states that no one cause of bronchiectasis seems capable of explaining all the situations that may be present and that it is almost certain that congenital factors may be involved. He finds no necessity for making a distinction between congenital and acquired bronchiectasis, since the factors which work to produce bronchiectasis of the acquired form probably are present also to produce the bronchiectasis of the so-called congenital variety. Infection and bronchial obstruction are the two major mechanisms involved. Since bronchiectasis may be associated with serious sinus infection, a careful examination of the nasal sinuses should be made to determine the presence or absence of inflammation, discharge, tenderness and clouding. When there is sinus infection plus bronchiectasis, the prognosis for surgical cure with lobectomy is less favorable. Beattie considers the only cure for bronchiectasis to be surgical excision of the affected lung tissue, which usually necessitates lobectomy. Considerable palliation can be afforded by medical management if the lesion is considered to be inoperable or if it seems unwise for any reason to try to cure the lesion by surgical intervention. Medical management of bronchiectasis consists of attempts to suppress the infection and keep the diseased lung free of secretions. Expectorants, postural drainage and other measures are suggested; however, there are disadvantages to each of these. He does not recommend the use of antibiotics except for serious infections, because through the development of resistant bacterial strains the antibiotics will lose their effectiveness in times of emergency. Even after pulmonary resection, it is believed that children under six years of age can grow new lung tissue. After this age, however, the loss of lung tissue is compensated for by the over-expansion of the remaining lung tissue.

The term "asthmatic bronchitis" is in frequent use in the pediatric nomenclature. Watson[147] found that the presence or absence of eosinophils in the peripheral blood stream was not of clinical significance in the patients studied. His present report is a series of twenty-three patients who were diagnosed as having asthmatic bronchitis during a period of five years. Of this original number, eight children eventually developed bronchial asthma. Skin manifestations of allergy have appeared in three children since the study began. In only two cases have the children or their siblings failed to show any allergic stigma up to the time when the report was published.

PNEUMOPERITONEUM

One of the most frequent and serious complications of bronchial asthma is emphysema, which may be acute or transient as well as chronic or permanent. It is recognized that occlusive bronchial changes completely disappear with the cessation of asthmatic attacks, which results in the escape

of air entrapped in the distended alveoli. This transitory or reversible form of emphysema is far from being benign or innocuous. Banyai[8] has named chronic infection of the lower air passages and aerodynamic trauma of frequent strenuous coughing to be two other important potent factors instrumental in the development of emphysema as a sequel to allergic bronchial asthma. In his opinion, the benefits derived from artificial pneumoperitoneum in the treatment of pseudohypertrophic emphysema may be listed as follows: (1) the elevation of the diaphragm which refunctionalizes this previously defunctionalized muscle; (2) the decompression of some large air cysts; (3) the intrapleural pressure becomes more negative; (4) a more even and widespread distribution of the inhaled air is made possible and thus better oxygenization of the blood is accomplished; and (5) the venous return from the periphery of the greater circulation to the heart is better facilitated.

He describes in detail the manner in which artificial pneumoperitoneum is accomplished under his direction and care. Failures from this procedure may be attributed to many factors, namely, the irreversible and extensive loss of alveoli and elastic elements of the lung, widespread pulmonary fibrosis, sustained bronchospasm, diaphragmatic adhesions, atrophy of disuse of the diaphragm, heart failure that cannot be corrected, and uncontrollable complications which interfere with cardiorespiratory function.

In order to diminish the stress on the right heart and pulmonary vascular bed before severe secondary cardiac disease can develop, Hurst, Levine and Rich[72] have treated twenty-eight patients with I^{131}. It was their impression that cor pulmonale is present in some degree in all cases of severe pulmonary emphysema. Their eventual procedure following the initial diagnostic study was to give 20 millicuries of radioactive iodine, followed in two months by another tracer study and an additional 20 millicuries of radioactive iodine. There has been a noticeable improvement in these patients as evidenced by a gain in weight, gain in appetite, a sense of well-being and an increase in exercise tolerance. Of the twenty-four cases, two had excellent results and eight had good results, although there were two later deaths. Nine cases had fair results, while the remaining five cases died early in the course of treatment in congestive failure. These latter instances represent the only poor results. The authors believe that treatment with radioactive iodine should be instituted before severe congestive failure supervenes with the inevitable termination.

Gordon[58] has reviewed the subject of emphysema stressing the geriatric aspects. Comparison is drawn between the emphysematous patient who usually prefers to lie flat and individuals with heart failure who assume the sitting position. Maximal breathing capacity seems to be more significant than vital capacity tests. Most important of all, however, were exercise tests. This author recommends the use of breathing exercises with the occasional addition of intermittent positive pressure breathing, abdominal suction or other procedures.

BRONCHIAL ASTHMA

Asthma in industry has been a subject that has attracted the attention of several authors during the past few years. Brown and Colombo[22] group the asthmatic working patients into three or four categories. They state that in some patients the working conditions are the primary causes of wheezing, while in others these causes are of secondary importance. Still other patients may have factors which nonspecifically aggravate their co-

existing asthma, or under different working conditions there may be no relation although the patient wheezes while at work. It is the duty of the plant physician to estimate the effects of the working environment when a patient presents himself with asthmatic complaints. There are many industrial causes for asthma, but their influence upon the individual patient is a particular problem.

ALLERGIC AND NONALLERGIC ASTHMA

The use of ephedrine with codeine to control the cough of asthmatic children has been recommended by Fontana.[51] The paroxysmal cough associated with asthmatic attacks in children is controlled by the combined use of these two preparations. Ephedrine is quite useful as a smooth muscle relaxant, and the effectiveness of codeine in controlling cough symptoms is well recognized. This author recommends careful judgment in the choice of drugs in treating asthmatic children.

Attention is called to the frequent occurrence of thickened basement membranes in nonallergic chronically diseased lungs. Crepea and Harman[31] believe that the thickened basement membrane is not a peculiarity of bronchial asthma alone. They have studied the tissues from 116 autopsies during a one-year period, as well as from 107 lungs removed surgically because of a variety of disease processes such as carcinoma, tuberculosis and bronchiectasis. In the lungs from the routine autopsies, 23 per cent had thickened membranes, whereas among surgically removed lungs an incidence of 32 per cent was found. The occurrence of thickened membranes in asthmatic patients was 100 per cent. Development of thick membranes in the mucosa of nasal polyps and of the sinuses affected by chronic sinusitis might also suggest a causal relationship in conditions where large quantities of acid mucopolysaccharide ground substances are elaborated.

Nonallergic bronchial asthma is a term applied to those asthmatic patients whose illness usually begins after the age of forty and in whom no specific allergic factors can be demonstrated by the usual test methods. Stuppy[135] finds that the differentiation between nonallergic and allergic bronchial asthma on the basis of age alone is not reliable. In both instances the symptoms may be chronic and perennial; the sputum may be purulent, viscid and gelatinous; and the lungs at autopsy may reveal bronchial obstruction by thick tenacious mucous. In the patient with nonallergic bronchial asthma, chronic emphysema or cor pulmonale usually is the ultimate cause of death rather than the asthmatic attack itself. Treatment for nonallergic bronchial asthma is entirely symptomatic since no specific etiologic factors have as yet been established. He advises the use of expectorants, bronchodilator drugs, antihistaminics, sedatives, oxygen and steroid compounds. Each of these is discussed by the author. As an emperical procedure, vaccine therapy is stressed.

With chronic nonallergic asthma a cardiac component must be considered, in the opinion of Hurwitz.[73] When acute infection is present in these patients, antibiotics are fundamental to the treatment and if chronic infectious asthma is present, antibiotic therapy must be prolonged for months or several years. Since the bacterial flora may change in these instances, the drug must be carefully selected, and the choice must be guided by sensitivity tests. Breathing exercises are recommended to overcome anatomic alterations associated with functional emphysema. This author considers the nonallergic type of bronchial asthma to be more con-

ducive to status asthmaticus than is the allergic type. In these nonallergic individuals single attacks are common but frequent recurring attacks are usually present in allergic individuals.

Some patients will have recurrent attacks of bronchial asthma, show numerous positive skin tests, and have no causal relationship between these factors and the appearance of bronchial asthma. Miller and Baruch[100] report a patient in whom no correlation between asthmatic attacks and exposure to reacting allergens was evident. By the institution of play psychotherapy with the child, good results were obtained which support their thesis that emotional interplay could be correlated with the asthmatic attacks of this patient. Their patient had the feeling that he was not loved, and when his anger at his parents on this account was blocked from expression by his fear, asthma would result. The appearance of asthma in this instance occurred quite independently of his exposure to the allergens for which he had shown good positive skin test reactions.

INFECTIONS AND VACCINES

Forman and Blatt[53] have satisfied themselves that the method of Blatt and Nantz, a procedure which will identify the specific strain of organisms to which the individual is allergic, is reliable for the diagnosis of bacterial allergy. It is of particular importance to apply this method of testing and treatment to the elderly patient with asthma, because it is in these instances that special benefit has been noted. In cases of so-called intrinsic asthma they have been able to identify the allergen in a number of patients and to determine that these cases were in fact instances of bacterial allergy. In atopic patients with complications by bacterial allergy, they have been able to isolate a specific desensitizing agent which gives results superior to those obtained by hyposensitization for the offending atopens alone.

In discussing the relationship of disease of the paranasal sinuses to bronchial asthma, Walker[99] demonstrates that roentgenograms do not completely manifest the actual degree of disease that is present. It is quite possible that negative sinus roentgenograms may be obtained in the presence of subsiding infection or subsiding allergic response. Again, roentgenograms showing thickened membranes may be noted in the absence of either infection or allergy. In this same forum, Lockey[99] asserts that the combination of thickened mucous membranes, edema and infection is present in most instances of so-called intrinsic asthma. In these patients, proper treatment of the sinuses, plus specific hyposensitization therapy and environmental control is always indicated. Infection is a definite cause of chronic bronchial asthma. Swineford[99] states there is much evidence to support the impression that sinus infection causes asthma. Though evidence supports this contention, no one knows how sinus infection causes bronchial asthma. Sinus infection alone or allergy alone, or more often both, may cause chronic bronchial asthma. The patient with disease of the paranasal sinuses and asthma would be improved with closer collaboration between allergists and rhinologists.

Further evaluation of C-reactive protein in bronchial asthmatic patients has been presented by Aaronson et al.[1] They have studied 201 children with asthma and forty-three controls. In the group of patients with infectious asthma were eight children who had suffered a recent upper respiratory infection, seven of whom yielded a positive CRP. In the same group, seven children were studied who had not had a recent upper re-

spiratory tract infection, and none of these gave a positive CRP. In atopic asthmatic patients, different results were obtained. Of forty-four with recent upper respiratory tract infection, forty-two had negative and two had positive CRP reactions. These findings would tend to point to bacterial sensitization as an explanation for the appearance of CRP in the group of children with infection asthma, since CRP occurs about ten times more often in asthmatic patients with a recent upper respiratory infection than in those without it.

TREATMENT AND COMPLICATIONS

The treatment of patients with bronchial asthma ultimately depends upon its cause. Bernstein and Klotz[11] emphasize the statement that emergency treatment is used to relieve only symptoms. The prime requisite of immediate therapy is the prompt and safe procurement of an adequate airway, for which they stress epinephrine as the drug of choice if given in proper dosage. Safe sedation is of great value in treatment of a patient with bronchial asthma, and the reader is reminded of the pitfalls that must be kept in mind with the use of steroid therapy. They discuss aids employed in the treatment of bronchial asthma, including aminophylline, expectorants, the use of oxygen, aerosol, fever therapy, mechanical respirators and breathing exercises. The best treatment for patients with bronchial asthma is prevention, treating the precursor state before asthma occurs. The eventual choice of a drug for the relief of asthma depends upon the particular paroxysm that presents itself. Perlman[106] states that most protracted attacks of asthma may be relieved by the use of antispasmodics, expectorants and sedatives. Adequate fluid intake is of the utmost importance. This author believes that iodides, though woefully neglected by many physicians, are still the best expectorants for the asthmatic patients. Of secondary importance is the use of sedation in the asthmatic patient who must first be relieved of his respiratory distress.

Hansen-Pruss[64] has reported his observations of seventeen adult patients. These individuals received the "Gay treatment" over a period ranging from two weeks to two and one-half years, but the so-called cure had not materialized for any of these patients. He has reported four of these patients in detail, three of whom had skin eruptions of varying extent due to the long-continued administration of inorganic arsenic. Two patients of this group of seventeen had abnormal tests compatible with liver damage. In the majority of instances, symptoms of gastrointestinal complaints usually appeared two to six weeks after the arsenic administration was instituted. One patient had laboratory and clinical evidence of renal damage; and although this was the only instance, poisoning with inorganic arsenic could not be clearly implicated. After the ingestion of inorganic arsenic, the material can be recovered from an individual's skin, hair and nails for an indefinite period of time. Hansen-Pruss emphasizes the lack of authenticated therapeutic reasons why inorganic arsenic should be effective in asthma, showing that the administration of this preparation, either in the form of Fowler's solution or as part of the "Gay formula," is deleterious. That the urine arsenic content usually indicates indirectly the degree of absorption of arsenic is again mentioned by this author.[65] Arsenic is not usually found in the urine in abnormal amounts four to six months after the administration of this chemical. None of the seventeen patients reported by this physician

showed physical evidences of damage to the central or peripheral nervous system, nor did they present any clinical or laboratory evidence of bone marrow changes. The seventeen patients reported here were not benefited by the administration of arsenic or by variations in the form of the Gay treatment.

Unexpected death in asthma has been reported in nine patients by Maxwell.[98] In each of these nine patients, the asthma had had its onset after the age of thirty years with the family history being positive for asthma in only two instances. Only one autopsy showed bronchopulmonary changes. Upon this basis Maxwell thought that psychologic factors were important in all instances, each of the patients showing a marked defeatist attitude almost from the beginning of his illness.

That death may occur in the asthmatic patients even though on cortisone therapy has been reported by Savidge and Brockbank.[124] One of the two patients reported had been on cortisone therapy for a period of five months but died in status asthmaticus. After each bout of previous status it had been necessary to increase the daily maintenance dosage of cortisone. Good response to corticotropin therapy had been noted in the second patient reported by these authors, but after ten weeks of cortisone therapy the patient died suddenly. Autopsy showed his bronchi to be filled with plugs of mucus, death having been caused by asphyxia.

DRUG SENSITIVITY

The number of articles dealing with new drugs which are submitted for publication far exceeds the available space in the allergy journals. An editorial[44] reveals that the flood of new agents on the medical profession has really revolutionized the treatment of many important diseases. Without attempting to discourage individual research or deprive investigators of due priority and noticeable advances, it has been suggested that worthwhile evaluation of the relative merits of new drugs is better accomplished by groups of experienced investigators than by the single physician. New preparations can be better evaluated when work is done as a committee, and the combined opinion is expressed in a single publication.

Leake[85] has classified allergic drug reactions as being localized, generalized—as in anaphylactic shock—or generalized with slight and chronic reactions. A complex, capable of cellular sensitization, may be formed by any chemical having a carboxyl, amino or hydroxyl group combining with various amino acids. Though allergic reactions may result from almost any therapeutic agent, such drugs as epinephrine, caffeine, cascara sagrada and general inhalation anesthetics are seldom the cause of sensitization. Though oral administration of the antibiotic drugs reduces the tendency to sensitization or allergic reaction, this author says that the routine administration of antibiotics may lead to serious consequences. In general, the management of drug sensitivity is a symptomatic procedure. After allergic symptoms have appeared, antihistaminic preparations are of little value.

Atwell and Prior[4] report two cases of allergic rhinitis due to para-aminosalicylic acid. Both of their patients exhibited fever, nausea and malaise when treated with PAS because of pulmonary tuberculosis.

During the course of this tuberculotherapy, the development of fever or any one of a number of allergic manifestations should suggest drug

sensitivity. Most of the drug reactions of this type will be of the latent variety with the reaction occurring seven to twenty-seven days after the administration of this drug. If the drug responsible for these reactions is continued, serious harm to the patient may result. With the discontinuation of the medicine the untoward reactions usually disappear quite promptly. Such was the instance in the cases reported by these authors.

More fundamental information is needed regarding new drugs in the opinion of Brown.[20] He considers that better tests for toxicity and allergenicity and a better controlled method for clinical evaluation are necessities. Because papers are published in conventional chronological order, reports of reaction from drugs appear too late and too long after damage has been done. He advises the results of basic research problems to be given wide publicity as quickly as possible in order that dangers may be recognized. Rasmussen[111] has reported two instances in which periarteritis nodosa developed as a result of iodide hypersensitivity, a condition which may develop in other patients with bronchial asthma treated with iodides. Though the occurrence of vasculitis is rare in patients on iodide therapy, it may occur more frequently than is suspected and go unrecognized by the clinician. Rasmussen postulates that the development of the periarteritis nodosa as the result of iodide hypersensitivity may result from the union of the agent with plasma protein, thus forming an antigen; or the stimulation of specific antibody production by this antigen may be a possibility; or the union of antigen with antibody may result in vascular damage. He was able to demonstrate skin-sensitizing antibodies to potassium iodide in the serum of one of the two patients reported.

Thrombocytopenic purpura has been reported following the ingestion of a quinine-containing drug. Steinkamp and his associates[131] found that a test dose of quinine caused a severe systemic reaction, with a drop in platelets to as low as 17,600. A normal volunteer was given 200 ml of the patient's blood after he had ingested a large dosage of oral quinine. About one hour later symptoms of systemic reaction were observed, with the platelet count dropping to 20,000. Administration of the quinine alone or the patient's blood alone to the volunteer did not produce any evidence of systemic reaction. As a part of the reaction picture in this volunteer, clinical purpura and prolongation of the bleeding time to eighteen minutes was observed.

Immediate loss of consciousness and death despite resuscitative measures was observed in a patient given 5 cc of Gantrisin® by the intravenous route. Acute pulmonary edema, characterized by frothy mucus in the bronchi and alveoli, was observed. It is the opinion of Burrell[23] that the fatal reaction may have been related to drug hypersensitivity. The patient had been given a similar dosage of this drug about two or three weeks prior to the fatality without any untoward effect. Spring[129] describes three patients in whom drug hypersensitivity is manifested by swelling of the interphalangeal joints. Inasmuch as the signs of allergic sensitivity to the drug recurred repeatedly in the same location of the body, it was his impression that this was evidence of a fixed eruption. The interphalangeal joints were apparently the most reactive portions of the body and acted as "shock organs" upon the administration of medication. The sensitizing agents in the three patients reported were sulfathiazol, penicillin and thyroid.

CHLORPROMAZINE SENSITIVITY

Jaundice has been the only serious side effect mentioned in the literature following the use of chlorpromazine. Hodges and LaZerte[69] add to this growing list with a patient who developed jaundice after chlorpromazine therapy. The jaundice failed to subside and granulocytosis developed prior to death. Their patient was a sixty-seven-year-old white housewife hospitalized because of acute epigastric pain, fever and chills. During the months preceding her admission, a diagnosis of leukemia had been suspected since a sternal bone marrow study had revealed a moderate lymphocytosis which was consistent but not diagnostic of chronic lymphatic leukemia. An exploratory laparotomy was done eight days following hospital admission. Because of postoperative nausea she was given chlorpromazine by intramuscular injection. It was later learned that this patient previously had been on oral chlorpromazine for a period of about three weeks in an effort to give her relief from itching dermatitis. Postoperatively, symptoms and signs of agranulocytosis developed within a few days. The pathogenesis of the jaundice in all cases associated with chlorpromazine therapy is obscure. Agranulocytosis is an uncommon complication of chlorpromazine therapy, and the author states that this may represent the fatal complication in their patient. The liver lesion was eventually identified as "intrahepatic cholestasis" without extrahepatic biliary obstruction.

Within five to ten minutes after receiving sodium dehydrocholate for measurement of circulation time, the patient of Sanchez and Morris[121] became severely dyspneic, cyanotic and then suffered tonic-clonic convulsions. Death occurred about forty minutes after the administration of the drug. One other fatality is reported by these same authors. In two other patients, symptoms and signs of a constitutional reaction were in evidence, but the patients survived. It is postulated from the evidence presented by these authors that patients with a history of allergy and those with right-left shunts may be vulnerable to the untoward effects of Decholin.®

DEMEROL ADDICTION

Between July 1, 1950 and September 30, 1953, 457 meperidine (Demerol®) addicts were admitted to the U. S. Public Health Service Hospital at Lexington, Kentucky. Sixty-three per cent of these patients were primary meperidine addicts and 37 per cent were secondary addicts. The chief reason for the onset of the addiction was reported to be either discomfort resulting from trauma, a chronic medical condition, or physical discomfort. The majority of these patients obtained their drugs from physicians. It must be remembered that persons who have never been addicted to opiates do become addicted to meperidine and have symptoms of abstinence after withdrawal of the drug. There is a high proportion of physicians, nurses and members of allied professions among the meperidine addicts, which may be due to the failure to appreciate the addictive properties of the drug. Rasor and Crecraft[112] report that the number of meperidine addicts admitted to this hospital has increased considerably since the introduction of the drug in 1944.

MEDICAL MANAGEMENT

Feinberg and Feinberg[80] have shown that sympathomimetics, bronchodilators, antihistamines, expectorants, sedatives, steroids and antibiotics may be used for relief of allergic symptoms. Though the antihistamines

have been popularly employed in the relief of childhood asthma, they are not generally useful for the relief of asthma in adults. These agents should never be used to replace epinephrine in the management of anaphylactic shock or the acute allergic reaction, though they may be used in good form as a supplementary material. In a similar vein, steroid therapy should not be considered as a substitute for other symptomatic treatment nor for adequate investigation and specific management of the allergic syndrome.

Rounds[118] reports six cases which demonstrate aminophylline toxicity. Excessive stimulation of the central nervous system, gastric irritation and effect on the kidney are discussed by this author. Toxic symptoms are discussed under the headings of headaches, confusion, restlessness, reflex irritability, spasms, paralysis, generalized convulsions and vomiting. In prescribing aminophylline the physician should be careful regarding the dosage, as this varies with the route of administration. There is great individual variability in the amount of drug absorbed. The possible toxic effect of aminophylline in children is also stressed by Love and Corrado.[87] Though aminophylline is a useful drug in the relief of asthmatic symptoms, they stress the early symptoms of toxicity to be unusual restlessness, recurring emesis and albuminuria. A dosage of 0.25 grams of aminophylline by rectal suppository is stated to be too large for infant administration.

MERCURIAL REACTIONS

The quantitative response to mercury preparations is in proportion to the dosage consumed, while the qualitative response is a pathologic change dependent upon sensitivity or allergy. Minute doses in these latter instances may produce severe violent local or systemic effects. Marshall[95] has shown that the qualitative or allergic responses to oral mercurial diuretics may be characterized by severe reaction even to the most minute doses. The symptoms may be of the local contact dermatitis type or of the severe systemic type with fever and skin eruption eventually leading to exfolliative dermatitis. With the administration of mercurial therapy it is necessary that the patient be carefully supervised, with each patient being instructed regarding the possibility of reactions and the length of time the drugs may be safely used. Brown[21] has stated that a number of reactions frequently attributed to mercurial diuretics are not truly due to the drug. He has shown that some so-called reactions are the result of diuresis, causing sodium, potassium, or calcium deficiency. A great number of fatal reactions which have occurred in the past were involved with the more toxic mercurial compounds. More cautious dosage schedules and a judicious awareness of the implications of early minor side reactions have led to surprisingly few fatal reactions from these drugs. In those patients whose history shows them to be "drug reactors," treatment with mercurial diuretics should always be initiated with a small dose. It is emphasized that intradermal skin tests or patch tests even on abraded skin are not dependable. Brown lists the types of reaction to be: local, oral, gastrointestinal, skin, renal, cardiovascular, bone marrow and systemic reactions. When no response is obtained from a mercurial diuretic, it should be discontinued until possible electrolyte imbalance is corrected. In the face of a sensitivity reaction to a mercurial, another preparation may be cautiously substituted. A minor reaction, though not a contraindication, suggests a smaller dosage or less frequent administration.

TRANSFUSION REACTIONS

In the past few years there have been several reports indicating that injectible antihistaminic drugs are useful in the prevention of allergic and pyrogenic blood transfusion reactions. Wilhelm[149] and his associates add to this growing list. They added 5 ml of diphenhydramine hydrochloride (50 mg) to 518 units of whole blood. Their control studies were completed with the addition of a similar amount of saline to 474 units of whole blood. The identities of the control and the antihistaminic preparations were withheld from the investigators until the transfusion reactions were evaluated. Results indicate that the effect of the diphenhydramine hydrochloride in the concentration employed is not unlike that of an equal volume of .9 per cent sodium chloride. The addition of diphenhydramine hydrochloride completely eliminated the allergic type of transfusion reaction but apparently had no effect on the incidence of pyrogenic reactions. The addition of the Benadryl® did not cause significant hemolysis. Both allergic and anaphylactic types of reaction are associated with blood transfusions, and are believed to result from the passive transfer of substances via the donor's blood. An urticarial rash, swelling of the mucous membranes, generalized itching and occasional nausea and vomiting are characteristic symptoms of an allergic type reaction. Anaphylactic reactions are suspected with the occurrence of the "shock syndrome" and a feeling of great apprehension by the patient. Both of these reactions are due to the release of histamine acting on receptor cells. Though many such reactions can be prevented by the administration of antihistaminic drugs, these preparations do not prevent the release of histamine but block its effect on the receptor mechanism of cells involved.

Stephen and his co-workers[132] employed Pyribenzamine® in a dosage of 25 mg of the drug to 1 cc of solution. Under sterile precautions 25 mg of the antihistamine was added to the blood just prior to transfusion. It was their conclusion that the antihistaminic drugs did afford protection against histamine liberating reactions. The addition of Pyribenzamine significantly reduced the incidence of pyrogenic reactions as well as the allergic type reactions, and they did not feel that the decrease in pyrogenic reactions was coincidental. They suggest that some of the reactions labeled pyrogenic may, in reality, be allergic in type. The efficiency of the drug, however, is less marked when it is administered therapeutically after a reaction has begun. Frankel[54] in a supplement to his original work has reported the results of a study of antihistamine in 1064 blood transfusions. In this present series, 361 pints of blood had chlorprophenpyridamine maleate added, and 111 pints of blood were used without this anthistamine. Immediately prior to the transfusion, 10 mg of the antihistaminic preparation in solution was added to the blood. Of the 361 transfusions with the added antihistamine, only one reaction occurred which represented an incidence of 0.3 per cent. There were no side effects attributable to the antihistaminic preparations. With the administration of 111 pints of blood with no added antihistamine, four allergic or pyrogenic reactions occurred, representing an incidence of 3.6 per cent. He concluded, therefore, that the addition of the antihistamine to blood for transfusion was a highly satisfactory means of preventing allergic and pyrogenic transfusion reactions.

ANTIHISTAMINIC PREPARATIONS

In reporting their observations on the clinical trial of a new antihistaminic preparation, Dutton and Halpin[39] agreed that the medication under

observation, labeled FC-1, compared very favorably with other well known and often used antihistaminic agents. They described their experiences with tropin-4-chlorobenzhydryl ether hydrochloride. Halpin administered this drug to eighty-one patients during the mold and ragweed seasons of 1953 with encouraging results, and found the antihistaminic action to be satisfactory and prolonged. In one instance there were side effects of a degree necessitating cessation of therapy. Dutton observed that the drug was particularly well tolerated in children and suggested that the dosage employed might profitably be reduced to eliminate side effects. It was noteworthy that a few cases which had consistently failed to respond to any other type of therapy and other antihistaminics did obtain an appreciable degree of relief from the use of FC-1. Neither author found any significant effect upon the formed elements of the blood with the administration of this new antihistaminic compound. Perhaps the best development in antihistaminics during the past year or so has been the increase in the length of time over which some of the newer compounds exert their action.

Landau and Gay[83] report their experience with a compound which, through a single dose protected guinea pigs against effects of histamine and prevented anaphylactic reactions for as long as one to three weeks. The compound with which they worked was 1-parachlorobenzhydryl-4-P-tertiary-butylbenzyl piperazine dihydrochloride. A single dose of this compound inhibited to a large degree the smooth muscle reaction to histamine in the Dale bath for at least five days. The drug also protected against death from intravenous histamine injection for as long as two or three weeks following the original administration of the preparation. There was a decrease in the response to histamine aerosol for three weeks or more after the administration of the preparation. There was a noticeable inhibition of the major effects of histamine aerosol for as long as four to nine days, and protection against death from anaphylactic shock was noted for twelve days in the pigs studied. The passively induced Arthus reaction, however, was not affected by the administration of this compound.

Twenty-four patients reported by Mallov[94] were given antihistamines parenterally while they were being treated for their pollen sensitivity. Ten of the patients received 10 mg of Histadyl® in close proximity to the injection site. The remaining fourteen patients were given 1-4 mg of chlor-tripolon in combination with the antigen in the same syringe. He found that it was possible to increase substantially the dose of pollen extract beyond the previous maximum level without constitutional or local reactions when the antigen was combined with antihistamine. Mild side reactions were present in about 40 per cent of the patients treated, but in no instance was it necessary to discontinue treatment because of these reactions. Accurate measurement of both the antihistamine and the extract can best be accomplished by making two injections rather than combining the materials in the same syringe.

In nine cases antihistamine therapy produced relief of the nasal symptoms treated, but produced asthma as a substitute complaint. This was the impression of Macaulay[92] during the investigation and treatment of 3,000 cases of allergic rhinitis over a four-year-period. With the cessation of antihistaminic therapy, the asthma was relieved and did not reappear.

Strauss and co-workers[133] recognize the fact that one of the most im-

portant side effects of antihistamines is their sedative action, and that controlled studies of their hypnotic effect are lacking. For their study they used methapyrilene hydrochloride. Patients were not accepted for inclusion in this study if they had acute physical symptoms which significantly disturbed their sleep, were placebo reactors, exhibited severe emotional disturbances, or required narcotics. The authors selected fifty-four subjects, the average age of whom was 52.2 years. Methapyrilene hydrochloride (50 mg), phenobarbital (100 mg), and a placebo were administered as capsules of identical appearance. The investigators were not aware of the specific contents of any particular capsule. They found that both methapyrilene and phenobarbital were more efficient than the placebo in their hypnotic effect. The patients seemed to favor phenobarbital, but the nurses' observations revealed that methapyrilene was more effective than phenobarbital in inducing sleep. They advised that necessary precautions should be used with the prolonged use of methapyrilene hydrochloride, even though there have been no recognized cases of agranulocytosis due to this drug. There were no complications nor toxic effects following the use of the agents employed in this study, but a more prolonged use would probably result in a higher incidence of complications. There seemed to be some tolerance developed for the sedative action when the antihistamine was used, being noticeable on occasion after the first few doses of the drug.

PENICILLIN REACTIONS

Winton and Nora[150] present three cases of acute penicillin sensitivity. Autopsy findings of one case showed serious myocarditis with round cell infiltration and generalized vascular endothelial necrosis. They postulate that the antibodies acting in penicillin sensitivity are of three different types—namely, one that is skin sensitizing, one that is anaphylactic, and the third which is a precipitating immune body responsible for the Arthus phenomenon. It is this latter type which also results in periarteritis.

There has been a noticeable lack of standardization for testing for penicillin sensitivity. Tuft and his associates[143] found a higher incidence of specific positive tests in those patients with a history of allergic reactions to penicillin. The positive skin test which is indicative of the presence of the anaphylactic type of allergy is temporary and may disappear within a short time. A positive skin test in these individuals is obtained when the interval between the occurrence of the reaction and the time of the testing is quite short. The most satisfactory means of skin testing for detecting penicillin sensitivity was the intracutaneous injection of .02 cc of a concentration of penicillin of 10,000 units per cc. It is wise to precede this intradermal injection by a scratch test. Positive patch test reactions are useful only in the diagnosis of a contact form of allergic dermatitis to penicillin. Such tests are without value in the anaphylactic forms. Delayed skin tests, whether intradermal or scratch, were not considered as reliable indicators. Symptoms of anaphylaxis in man are more frequently due to edema rather than to contracture of smooth muscle.

Berger and Eisen[10] undertook a study to determine whether testing by any method could prevent anaphylactic reactions to penicillin. They tested allergic patients, nonallergic individuals and a group of penicillin-sensitive persons with both recent and remote reactions. Both scratch and intradermal testing were done with controls being given at the same time. One thousand persons given penicillin tests showed twenty-four positive reac-

tions and 976 completely negative reactions. Of the twenty-four positive reactions, no relationship was noted to the three groups tested. In fact most reactions occurred in the group of nonallergic individuals. The authors, therefore, feel that testing is not a reliable way to ascertain penicillin sensitivity.

Lapin[84] has reported that a review of the literature shows intramuscular injections of penicillin are rare causes of any fatal or near fatal anaphylactic reactions in pediatric practice. No severe or serious reaction has been reported due to oral penicillin in children. This author studied 402 children who were routinely given oral penicillin-G tablets. He reported only 0.5 per cent mild urticarial reactions among these patients, with no major reactions being noted. He therefore advised the routine use of oral penicillin in an effort to avoid the complications of upper respiratory infections in infancy and childhood. There was the theoretical objection that these children studied by Lapin are potentially becoming sensitized to penicillin and may have reactions in adult life. He answers this objection by stating that the choice should be made between the statistically rare possibility of producing sensitivity to penicillin and the statistically frequent occurrence of severe complications such as otitis, mastoiditis, rheumatic fever or glomerulonephritis in the untreated upper respiratory infections of childhood. Some aspects of the above report are highly controversial. It is editorialized[45] that most allergists would agree with Lapin. When penicillin is given to children, there is very little likelihood of their having a serious reaction. The controversy arises, however, when one uses penicillin as prophylaxis routinely in respiratory infections in infants and children. It is questionable whether it is worth while to give penicillin routinely in all of these infections in the hope of preventing the complications of nephritis, otitis and mastoiditis, but at the risk of having the complication of penicillin sensitivity. It is this reviewer's impression that the physician should use one of the antibiotics that can be given orally, reserving penicillin for those rare instances where it may be the only antibiotic of value. However, in recent years the introduction of new antibiotics has made this picture a very changeable one.

In the opinion of Matheson and Elegant,[96] anaphylactic reactions following penicillin administration to children are scarce, but such reactions do occur and are not uncommon. They skin tested 400 patients, including 397 children, first by scratch test and later by intracutaneous tests. One positive test to penicillin in the entire group was obtained. Ninety per cent of the children tested had previous penicillin contact by various routes of administration. In these children tested, they found nineteen positive skin tests to *penicillium notatum*. They were unable to demonstrate any positive skin tests for procaine. In one group of six children who had experienced severe constitutional reactions following the administration of penicillin, four of the five children who had had immediate or accelerated reactions had immediate positive skin tests to penicillin. Two of the patients had positive passive transfer skin tests. The authors were unable to find any correlation between dermal sensitivity to penicillin and that to *penicillium notatum*. They concluded that an immediate positive skin test with penicillin in children who have had penicillin contact is indicative of the presence of potential clinical sensitization. If it is necessary to give penicillin to these children, the oral route of administration is advisable.

Most of the time the use of antibiotics is associated with no significant toxic effect, according to Kagen and Faller.[78] The allergic reactions most

frequently seen, however, are "serum sickness" with urticaria, edema, and pruritus. The anaphylactic type reaction occurs most frequently in persons who have shown previous sensitivity to the antibiotics, but there are reported instances of patients with this reaction in whom no such history can be obtained. Systemic reactions are discussed by these authors with the main items of interest being directed toward the gastrointestinal or neurologic systems, blood dyscrasias, renal and liver involvement, and accidental reactions. Important in their discussion is the information that vitamin K and various members of the B-complex group are normally synthesized by the bacteria which constitute the normal intestinal flora. Since broad spectrum antibiotics can eliminate large numbers of these bacteria, the resultant deficiency of vitamin K and B-complex is a serious problem. An even more complicated situation will arise when diarrhea or vomiting follows the use of antibiotics. They state that infants and children in general will have fewer reactions than adults.

Alarming symptoms of intense apprehension and fear of impending death followed the intramuscular injection of one million units of procaine penicillin-G to the patient of Sharon.[125] The reaction, fortunately, was nonfatal but quite serious. This patient had received previous injections of penicillin in the treatment of symptomatic neurosyphilis. Emergency treatment brought about the relief of the acute symptoms, but the patient continued to complain of weakness for a period of the following two weeks. Lowell[89] advises that incidental and unnecessary exposure to sulfonamides and antibiotic drugs should be held to a minimum. It is preferable, according to this author, to give short-acting, rather than long-acting, preparations to those individuals who have had allergic reactions to a drug in the past or who are believed to be prone to develop reactions. He also advises the administration of these preparations by the oral route. Lowell states that the appearance of a drug rash will usually be promptly recognized, but it is more difficult to recognize the involvement of the vascular, renal, hepatic or blood-forming systems as part of drug sensitivity. He believes that severe infection may tend to induce a state of tissue unresponsiveness to allergenic stimuli and that acute infections may also induce increased activity of the adrenal cortex. These two points are used to explain the low incidence of drug reaction in acutely ill patients.

OTHER REACTIONS

Erythema, urticaria and generalized pruritus were part of a reaction following one dose of tetracycline. Welsh[148] noted that these signs and symptoms developed at sites of previous eruption from the use of chlortetracycline and were accentuated after the use of oxytetracycline. He postulated that the tetracycline group was responsible for the crossed fixed drug eruption from these three antibiotics. Reactions following the unintentional administration of penicillin to sensitive patients have been reported by Coleman and Siegel.[27] They point to the contamination of syringes as the most likely possibility of this occurrence. In their patient, extremely sensitive to the antibiotic, a severe reaction occurred. Investigation showed that the sterilizer water in which the syringe had been boiled was found to contain penicillin antigen in appreciable amounts. They consider this a logical explanation for the patient's severe allergic reaction to the injection of testosterone and procaine. They were unable to elicit positive reactions by direct test with testosterone and procaine on this patient when uncontaminated syringes were employed. To reduce the

likelihood of contaminating syringes and sterilizers with penicillin they considered it imperative that all glass syringes and needles be washed at least three times with running water after their use. The syringe parts should then be separated before they are placed in the sterilizer. As a result of their experience, they suggest that separate syringes and a separate sterilizer be used for those syringes that will be used in the administration of penicillin. It might be easier to use disposable cartridges in connection with penicillin administration.

Mosko, Nejedly and Rostenberg[101] found the most satisfactory criterion for determining the likelihood of a dangerous reaction following penicillin administration to be the history of any kind of reaction on previous use of the drug. The mere performance of a skin test in an extremely sensitive person may lead to a serious or even fatal reaction. Penicillin-O cannot be substituted for penicillin-G in the penicillin-sensitive patient. They found no correlation between cutaneous reactivity to penicillin, either O or G, nor to *penicillium* or *trichophytin*. Though the presence of positive skin test reactions to penicillin does not necessarily indicate systemic sensitivity, it should serve as a warning to avoid the administration of penicillin to that patient.

ENDOCRINES

The intravenous administration of 50 mg of hydrocortisone per hour produced no untoward effects in fifty instances as reported by Rukes, Orr and Forsham.[120] They recommend that supplemental doses of cortical hormones should be supplied either orally or intramuscularly following the intravenous use of the drug. The dosage may gradually be decreased thereafter. The intravenous use of hydrocortisone should not replace standard and proved methods since the reported route is a short term, intensive method of therapy. It has been estimated that 93 per cent of the hormone is eliminated from the body within twenty-four hours after the intravenous administration; thus the tendency for untoward reactions is diminished. Grater[59] reports on the availability of hydrocortisone for intravenous administration. He gave this preparation to his patients by adding 100 mg (in 50 per cent alcohol) to 1000 cc of 5 per cent dextrose. The rapidity of administration was stated to be 50 mg per hour without any untoward effect. All six patients reported by this author showed significant eosinopenia within six hours. The vital capacity and maximal breathing capacity changes closely paralleled each other; and, as was expected, the changes in maximal breathing capacity were much more dramatic. Grater states that the intravenous hydrocortisone is an effective and swiftly acting therapeutic agent in asthmatic patients. It is the therapy of choice in acute adrenal cortical insufficiency. The most useful application of intravenous hydrocortisone is in those situations in which speed and maximal effect are of utmost importance.

Wolf and Hightower[152] review their clinical experience with natural and synthetic endocrine products. Patients receiving these preparations vary tremendously in their response so that no rules can be adopted for hormonal dosage. The smallest effective dosage is stated to be the best one except in the treatment of cancer. In order that the physician may become familiar with a few hormonal preparations, the review by these authors is highly recommended.

The use of ACTH and cortisone is not recommended in those conditions where the standard methods of symptomatic relief are effective. Collins-

Williams[28] advises that the steroid preparations should not replace the accepted methods of antiallergic therapy, and indicates that these drugs should be used in childhood asthma in the treatment of the acute attack, especially status asthmaticus, for long term management in severe cases while waiting for accepted antiallergic therapy to become effective, and for the rare patient who does not respond to the usual antiallergic therapy. The use of steroid therapy in childhood eczema should be a temporary measure, employed to control a severe exacerbation of the disease or to clear the skin temporarily in order that investigative procedures can be accomplished.

Rohen[116] found the use of hydrocortisone suspension to be very satisfactory in the management of allergic and infectious rhinitis. No untoward side reactions were determined nor was any tolerance to the hydrocortisone suspension observed after continuous use of the preparation. The entire picture of allergic and infectious rhinitis is changed by the tissue response to the topical application of hydrocortisone suspension. Rohen made no attempt to vary the dosage from patient to patient and did not find it necessary to add an antibiotic to the drug in treating those patients with infectious rhinitis, nor to add an antihistamine to the preparation when treating a patient with allergic rhinitis.

Two cases of osteoporosis due to prolonged cortisone and corticotropin therapy have been presented by Eisenstadt and Cohen.[46] These cases are reported in detail. In osteoporosis the difficulty is a deficiency in protein metabolism rather than in calcium and phosphorous metabolism. Advanced age, menopause and restricted activity are factors which predispose to osteoporosis. They advise urinary calcium excretion studies to be performed serially and routinely. Determinations in excess of 150 mg per day point to a negative calcium balance. In addition to hormone therapy in these patients a high protein diet should be given and actively encouraged, but it is not necessary to add calcium to the diet. An unusually high incidence of peptic ulcer development in patients receiving steroid therapy has been reported by Bollet, Black and Bunim.[16] Serial x-ray studies were done at six weeks' intervals on eighteen patients receiving steroid therapy. Peptic ulcer developed in three patients. There was no appreciable relationship between the appearance of the ulcer, the duration of therapy or the dosage of the drug that was given. The ulcers were asymptomatic. Radiologic evidence of healing was noted within three weeks in each case following the usual medical regimen for peptic ulcer. It is necessary to observe carefully the patients receiving these drugs in order to prevent sudden perforation or hemorrhage. Addition of aluminum hydroxide gel to patients receiving the newer steroids is advised by these authors.

WITHDRAWAL SYMPTOMS

Cortisone therapy was abruptly discontinued in nineteen patients with asthma. Henneman and his co-workers[67] noticed the development of headache, nausea, vomiting, restlessness and muscle and joint pain in almost all of these patients, the symptoms subsiding spontaneously after two to five days. Though the cause of these symptoms was not apparent to the authors, they discuss the syndrome following the abrupt cessation of prolonged cortisone therapy. The onset of a rapidly worsening headache was noted about twenty-four to forty-eight hours after the last oral dosage of cortisone. The symptoms as above noted increased in severity for several days and then rather promptly waned and disappeared entirely without

any other therapy. In one patient the mild withdrawal symptoms were followed by collapse, nausea and violent nystagmus, suggestive of acute labyrinthitis. Upon the belief that the withdrawal symptoms might be of adrenal insufficiency, six of the patients were given daily intravenous infusions of 500 cc of 0.9 per cent saline solution for one to three days without any appreciable effect or amelioration of the symptoms. The authors noted the similarity between the symptoms of the withdrawal syndrome and those of mild adrenal crisis.

A patient with undiagnosed generalized dermatitis of three months' duration was under the care of Hill and Swinburn.[68] Acute anaphylactic shock followed an intramuscular injection of 25 units of bovine corticotropin, and fatality eventually occurred about eight days following the administration of the steroid. The autopsy report suggested the cause of death may have been brain damage secondary to the cerebral anoxia which occurred during the anaphylactic shock. The patient had been hospitalized on one previous occasion, receiving 10 units of porcine ACTH every six hours for twenty-seven days, and then 25 units every six hours for the following six days. He was then discharged from the hospital and on the following day received a slight reaction from the administration of ACTH. Nine months later he had a severe reaction from the administration of 25 units of bovine corticotropin. The onset of the reaction was noticed about ten minutes after the administration of the preparation. A negative passive transfer reaction to bovine ACTH was obtained. It is postulated by these authors that the anaphylactic reactions resulted from sensitivity to ACTH of a nonspecific type.

ECZEMA

A frequent problem in diagnosis and treatment is the patient with eczema. Regardless of the age of the patient, eczema is the same disease in all age groups. The differential diagnosis is not a problem. Bookman[17] states that contact dermatitis has been mistakenly associated with eczema because of the frequent use of the misleading synonym "contact eczema." The contact lesion does not strictly represent an allergic phenomenon except in the most local sense. The characteristic location in relation to some contact and the history is the basic difference in the majority of cases. He emphasizes that the value of skin tests should not be minimized. Though great emphasis is placed upon the allergy history, skin tests become a potent factor in the ultimate long-range treatment of the causes of the eczema. His experience indicates that the elimination diet cannot be related to the known facts of allergic disease and therefore does not supply the answers being sought as to the cause of the eczema. Basic symptomatic treatment of eczema should be based upon an understanding of the factors that potentiate the pruritus, both in the skin and in the patient himself. The removal of crusts and scales by bathing and the use of an ointment to lubricate the skin are two important features of local treatment. Bookman considers the inhalant group of environmental materials to be equal to, and sometimes more important than, foods as a cause of eczematous lesions. This impression is carried to the point where recommendation is made for desensitization for those environmental factors which cannot be adequately removed.

HAND DERMATITIS

Eczema of the hands constitutes a large percentage of partial and total disability among persons having skin diseases. Bluefarb[15] suggests that

the etiology of hand eczema is multiple and varied. The lesions of hand eczema may consist of vesicular, scaling, oozing, weeping, crusted or infected lesions. With certain reservations, 95 per cent of all cases can be included in five cutaneous entities, namely, contact dermatitis, eczematoid ringworm, sweat retention syndrome, atopic dermatitis and nummular eczema. Each of these is discussed in detail by this author. So-called "housewife's eczema" is really nummular eczema precipitated by the chemical action of soap and alkalis. Thus the constant immersion of the hands in water tends to produce deleterious and macerative changes. Important, too, is the reduction of emotional excitement. This can readily be accomplished by the use of Thorazine® in doses of 10 mg following lunch and dinner.

Jambor and Suskind[75] have made an appraisal of the role of soaps and detergents in the production of hand dermatitis in fifty-seven patients. No specific reactions could be elicited with commercial soaps or synthetic detergents. In seventeen of the subjects, the primary etiologic factors were discovered. These included nickel, rubber, petroleum fractions, dyes, lanolin, some drugs, perfumes and other materials. In five patients, specific contact sensitivity was superimposed on previous cutaneous conditions such as atopic dermatitis or dyshidrosis. The wide variety of lesions was considered as evidence that hand dermatitis is filled with pitfalls because of the changes in morphology. In a subsequent publication, Jambor[74] studied the irritative action of synthetic detergents and soaps on hand dermatitis in twenty-two subjects. The right hand of each subject was immersed for one-half hour in a bath containing 0.5 per cent concentration of soap or detergent solution. The left hand was used as a control, being immersed in tap water of the same temperature. In no instance was the author able to elicit a persistent irritative effect by soaps and detergents. However, the failure to find reactions may have been due to the infrequency of immersions as well as the lack of mechanical irritation.

A significant number of cases of hand dermatitis are produced or aggravated by inhalant allergens in the opinion of Jillson and Piper.[76] There is a marked difference in the amount of allergen required in the process of desensitization of atopic dermatitis as compared with the amount required in respiratory allergic diseases. The amount of antigen used in skin testing for the delayed type of allergy is usually greater than that used in testing for the immediate wheal type of response, thus resulting in a flare-up of the dermatitis as the skin test becomes positive. In treatment of these patients these authors used extremely dilute antigens given in fixed amounts and usually self-administered by the patient. Their dosage was judged by the amount which would not produce a local reaction or a systemic flare when injected intradermally. Treatment was instituted at twice weekly intervals until there was a clearing of the dermatitis, after which the interval between injections was increased. Finally a so-called booster shot was given every three to four weeks. It was necessary in all of their fourteen reported cases to continue the desensitizing treatment for twelve months or longer. They suggest that in view of suspected failure the addition of staphylococcus antigen to the other extracts will be of value.

Alden[2] defines an industrial dermatitis as any inflammatory disease of the skin in which occupational exposure can be shown as a major cause, either contributory or eliciting. Predisposing factors which may set the stage for the development of an industrial dermatitis have been listed as

race, type of skin, sweating, age, sex, season of the year, cleanliness and other existing skin diseases. Industrial dermatitis may be produced by direct action of a chemical on the normal skin at the site of contact. It may also be produced by an agent which, on first contact, produces no demonstrable change, but on later and further contact produces an eruption at the contact site or even in distant portions of the skin. Alden reports that the large majority of cases of occupational dermatitis are due to primary irritants, while allergenic substances such as plants, dyes, rubber and other factors were responsible for only 20 per cent. Among the patients who show dermatitis from finished materials, however, allergy is the most frequent cause of skin eruptions. The attending physician must relieve, change or remove the causes and effects of industrial dermatitis.

CONTACT DERMATITIS

Contact dermatitis due to the ether soluble portion of tree pollen oil is a very unusual condition. Lovell and associates[88] present two patients in whom contact dermatitis was seasonal. The exposed areas of the skin were involved, and the lesion was indistinguishable from other types of dermatitis venenata. Positive patch test reactions to the tree pollen oils were observed in both instances, and skin testing with the aqueous pollen extracts by both scratch and intracutaneous methods did not confirm the protein sensitivity. They suggest that testing for possible sensitivity to plant pollen oils in dermatitis venenata should include representatives of the tree pollen oils.

Treatment of plant contact dermatitis with oral administration of the specific oleoresin extract is an accepted procedure. Brachman and Roy[18] patch tested sixteen of nineteen patients and scratch tested eighteen of these patients with the oleoresin extracts from common local weeds, grasses, trees and flowers. Nine of the sixteen patch-tested patients had positive reactions, with five patients having positive protein-sensitive-type skin reactions from scratch tests. All of these nineteen patients were treated with oral administration of the specific oleoresin extract. The most common complaint with treatment was pruritus ani. Some patients experienced mild lesions of urticaria. Definite improvement was experienced by six out of nine contact sensitive patients, and two of the skin test sensitive patients reported improvement. The authors report that oral hyposensitization is beneficial in those patients sensitive to the oleoresin but not to the protein fraction of the plant. Cronk and Naumann[33] were unable to influence the progress of poison ivy dermatitis with a 4 per cent lotion of hydrous zirconium oxide. The lotion was applied prior to the expected exposure to poison ivy plants. Some protection against poison ivy dermatitis was afforded by the application of this lotion.

During a panel discussion at the Southwest Allergy Forum in Houston, Texas, in 1955, the question was asked whether the drug, chlorpromazine, could be considered as a cause of contact dermatitis. The answering panel member was of the impression that chlorpromazine should be considered as a possible agent of contact dermatitis. Lewis and Sawicky[86] report two patients in whom severe incapacitating skin reactions to chlorpromazine had been noted. Prolonged handling of the drug, which results in frequent or overexposure by contact, seems to be a factor that predisposes to the appearance of contact sensitivity from this agent. It is necessary to recognize the causal agent and to institute prompt suitable measures to prevent further contact.

The chief difference in action between hydrocortisone and fludrocortisone is quantitative rather than qualitative. Robinson[115] compared the two preparations in patients whose conditions had been shown to respond to hydrocortisone. Forty-four patients were treated with lotions containing 0.1 and 0.2 per cent concentrations of fludrocortisone. A better response was noted with hydrocortisone lotions than when ointments of similar concentration were employed. However, the fludrocortisone compound was superior after forty-eight hours' observation. No serious toxic symptoms were attributed to fludrocortisone over a ten to fifteen-day period when administered to two patients. The author estimated that fludrocortisone had about twenty-five times the therapeutic potency of cortisone.

Baer and Schwarzschild[5] have been concerned with dermatitis and pruritus which tend to be more difficult to control in older individuals. These patients received more medications for various illnesses, and many of these medications are considered as potential sensitizers. In geriatric practice, drug eruptions are fairly frequent, probably because of the number of medications to which these patients are exposed. Less frequently noted are atopic dermatitis, allergic eczematous dermatitis and others. Chronic urticaria is a major problem in individuals over the age of fifty and may persist for as long as two or three years after complete elimination of the cause. Penicillin reaction urticaria has been shown to exist for as long as eighteen or twenty months in older individuals. The causes of urticaria in the geriatric patient may be found among drugs, food, foci of infection, intestinal parasites, inhalant allergens, physical agents or emotional factors. Thorough examination is necessary to find the cause, and skin tests are of little if any value in this search.

Baer and his co-workers[6] conducted experiments to answer the question whether foot bath water contaminated with pathogenic fungi was capable of causing acute attacks of dermatophytosis. They studied sixty-eight subjects whose feet were both microscopically and culturally negative for pathogenic fungi. A subject with proved fungus disease of the feet was allowed to immerse both feet for fifteen minutes in a sterile basin containing 200 ml of sterile tap water. Within the following thirty minutes an uninfected volunteer (one of the above sixty-eight) placed his right foot into presumably contaminated foot bath water. The left foot, serving as a control, was placed in another basin containing 200 ml of sterile tap water. The number of viable fungus particles per 200 ml of foot bath water averaged 295,000. Not a single instance of clinical fungus disease was produced among sixty-eight volunteers exposed under such conditions. During the six weeks after this fungus exposure, mycelia were found on one or both feet of 54 per cent of these volunteers. These authors suggest that public health and individual measures for prevention of active attacks of fungus disease of the feet should be based on maintenance and increase of local resistance to the infection rather than on useless measures designed to prevent infection.

LOCAL TREATMENT

In the local treatment of allergic dermatitis the most important principle is to reduce the present inflammation. Elimination or reduction of infection and pruritus is of secondary importance. Haeberlin[60] considers eczema, urticaria, purpura and erythema multiforme to be allergic dermatoses. The first step in topical therapy is to choose the vehicle or physical state which the application is to assume. Solutions with water as the

vehicle are useful in general for very acute inflammatory dermatoses with or without weeping. Treatment with compresses, baths or shake lotions often lead to excessive drying with subsequent itching, scaling and fissuring which must be overcome by the use of an emollient. As a rule, dermatologists put more emphasis on the history and less on testing, in order to determine allergic factors responsible for skin diseases. Haeberlin considers the use of internal administration of antibiotics to be rational therapy for the elimination of focal infections not amenable to surgical treatment. Also accepted by this author is the attempt to desensitize the patient by means of vaccine or specific protein extract administration.

It is the opinion of Gaul[56] that the most common and most frequently overtreated of all dermatoses is contact dermatitis. Since this is a symptomatic diagnosis, it is usually solved by searching out the causative factor. The areas of the skin most subject to trivial trauma and contact dermatitis are the most common sites for primary sensitization dermatitis from such things as mercurial antiseptics. In establishing a diagnosis of overtreatment dermatitis it is important to know the history of the onset of the lesion, rash, irritation infection or injury. It is necessary, too, to have a complete account of all remedies applied and the sequence of their use. It is not unusual to find the same therapeutic materials in the remedies producing local flaring, spreading and generalizing of the dermatitis. Primary sensitization signs appear on the skin at the site of the ointment or lotion application. The appearance of vesicles or pustules is the cardinal sign of beginning sensitization. This must be recognized in its early stages in order to prevent it from becoming more wide spread. Secondary signs appear when the sensitizing treatment chemical is in continual contact with the primary sensitization area and especially if the treatment includes the area of spreading. These secondary signs may be urticarial, vesicular, "ids," blotchy or diffuse erythema or a patch of vesicles with coalescence and bullae. The appearance of pustules is considered a common secondary sign. Severe test reactions are common in the presence of secondary sensitization signs, and patch tests should not be done at this stage of the complaint. In another publication, this same author[57] found the highest degree of sensitization from treatment materials to be in the organomercurials and antibiotics. These two, instead of favoring healing by obviating infection, seem to delay healing in that they produce tissue damage in which infection could take place. An important aspect of the subject of overtreatment dermatitis is the tremendous number of topical drugs inducing therapeutic sensitization. In recent years powerful therapeutic sensitizers have replaced former innocuous ingredients such as calamine lotion, Lassar's paste and other preparations. Gaul advises that physicians restrict their treatment to a relatively small number of therapeutic agents with a low sensitizing index; if they wish to use an ointment that is likely to be a sensitizer, pretreatment patch testing should be done.

FOOD SENSITIVITY

The frequency of food allergy as a most important mechanism in the production of various allergic disorders is called to the attention of the general practitioner by Rood.[117] He emphasizes the cyclic occurrence of attacks and a history of food allergy in other members of the family as being of utmost importance, and has no faith in skin testing for foods in an effort to determine the causative substances. The most fertile diagnostic source is a detailed history and study by means of elimination or trial

diets. Further evidence that skin testing for food sensitivity may be misleading and certainly without value has been brought forth by Tuft, Ettelson and Schwartz.[144] The hypertrophic rhinitis of a chemistry student was noticeably aggravated by the odor of hydrogen sulfide and frying eggs. Skin tests were negative except for a positive reaction for house dust, but treatment with this extract was without benefit. Subsequent elimination diets demonstrated the presence of a clinical sensitivity for egg inasmuch as the patient showed considerable improvement on an egg-free routine. Other offending foods were discovered. After the elimination of these the patient remained symptom free as long as he maintained his rigid dietary program. Subsequent testing with methionine and cystenine, which are sulphur-bearing amino acids, produced interesting findings. One gm of methionine taken three times daily produced the same symptoms as eggs; thus, the correlation between the sulphur content of some foods and their tendency to provoke symptoms has been demonstrated. It has been suggested by these authors that the reaction is probably a biochemical rather than an immunologic procedure.

POLLEN AND COLITIS

Over the past fourteen years it has become increasingly apparent to Rowe, Rowe and Uyeyama[119] that pollen allergy is a substantial cause of chronic ulcerative colitis. In a study of several controlled cases they found pollen allergy to be the sole cause of at least three individuals suffering from chronic ulcerative colitis, and pollen allergy as a major allergic cause was also demonstrated in other cases under study. It seems probable to them that chronic ulcerative colitis may be the only manifestation of pollen allergy, just as nasal mucosa changes are the single manifestation in hay fever. Skin tests by the scratch method, though frequently indicating the presence of pollen allergy, may be negative in these individuals. The investigators omitted intradermal tests with pollens in these patients with chronic ulcerative colitis because of the possibility of exaggerating the existing symptoms. Confirmation of pollen allergy as a cause of these intestinal complaints depended upon successful desensitization therapy, as in other manifestations of pollen allergy. At times food or drug allergy may be associated with the pollen allergy. These are considered as contributing causes of the chronic ulcerative colitis. Need of surgery will become infrequent, according to these authors, with proper control of food and pollen allergy, along with indicated antibiotics and other adjunctive therapy. During the past seven years the authors have found it necessary to resort to surgery in only one cooperative patient. One other surgical procedure was done in an individual who was well controlled, was sensitive to food, but had perforation of the sigmoid after being on cortisone for a period of two weeks.

MILK REACTION

Some infants may be very acutely sensitive to a food protein. Collins-Williams[29] reports one case of acute nonfatal allergic shock to cows' milk, and concludes that the infant under his care was actively sensitized *in utero*. The patient had not received any cows' milk in the newborn nursery or at home until about two months of age, when he had severe vomiting and diarrhea following the ingestion of evaporated milk. The patient then had no further milk until a similar reaction at the age of six and one-half months. Collins-Williams suggests in prevention that

the infant should be breast fed from the time of birth, and that occasional supplementary feedings of cows' milk never should be ordered. However, if it is found necessary to use cows' milk as a supplementary feeding, this should be given in the form of evaporated milk and continued daily. After all symptoms of milk sensitivity have subsided, the infant may be started on an oral hyposensitization program with drop doses of pasteurized milk which has been boiled for three minutes, increasing these gradually but as fast as possible without precipitating symptoms.

SOY SUBSTITUTES

Ratner and Crawford[114] have undertaken a study of soy bean as a milk substitute from the standpoint of its allergenicity. Their present work presents the study of the anaphylactogenicity of soy bean in the guinea pig. The materials used were raw dried soy beans, soy bean flour and soy bean extract. They did not find any instance of sensitization in a large number of animals after a single sensitizing dose followed by an intravenous challenging dose. They were further unable to sensitize animals in which, instead of a single infection, as many as four sensitizing injections were given. The allergenic weakness of soy bean was demonstrated by these workers in their finding that an anaphylactic dose could only be caused by the addition of an adjuvant to reinforce the antigenicity of the material. The authors were unable to sensitize the guinea pigs by inhalation of soy bean flour, as the animals did not respond on subsequent inhalation experiments nor to subsequent intravenous injection of soy bean extract. As a result of their experiments evidence is presented that soy bean is innately a weak sensitizing protein. They maintain that the reduced amount of methione present in the soy bean may in part account for the lowered antigenic activity of soy bean.

Blue[14] has reported a folklore remedy for soy bean diarrhea. In twenty-five cases of soy bean diarrhea in infants and children who were allergic to cows' milk, this author found that Canada fleabane was used with good results, after the usual remedies had failed. The leaves of the plant, Canada fleabane, are dried and cured by spreading them out thinly and evenly in a well-ventilated room. A pinch of the dried leaves is then taken and placed in a receptacle to which hot water is added, similar to the fashion of making a cup of common black tea and in about the same proportions. This was then strained and added to the soy bean formula used by these infants. The dosage was variable, in that if the initial amount did not stop the diarrhea, the portion was increased in size and strength. The diarrhea of all of the patients cleared promptly and without any complications. After a period of several weeks to three months all of these patients were able to tolerate soy bean milk in the normal strength and formula without having diarrhea when the herb was removed from the formula.

ALLERGY AND PULSE RATE

In discussing idioblaptic allergy, Knight[81] has shown that the specific tachycardia is a reliable diagnostic point. Good reliance is placed primarily on avoidance of foods, drugs and inhalants found to produce both the symptoms and the tachycardia. The symptoms associated with idioblaptic tachycardia may be negligible or they may be prostrating and of serious import. One of the most outstanding symptoms is overwhelming unexplained fatigue that is present in these patients. They may be exhausted upon awakening in the morning, or tiredness may appear a short time after breakfast. Atypical headaches, neuralgias and myalgias

palpitation, hypertension, extrasystoles and a rapid pulse may simulate a psychoneurosis. The other symptoms are multiple. In investigating these individuals all patients are requested to fill out forty-eight-hour pulse charts. Preliminary pulse charts may suggest the elimination and subsequent testing of certain foods. If the pulse drops to normal after meals, stable foods may be tested separately between meals or in the evening. Single foods may be taken six or eight times daily and the pulse charted for each one. Rarely a complete fast may be indicated. Other pulse accelerating factors listed by this author are virus infections, emotional crises, exercise or anxiety neurosis. He considers that the presence of nonreagenic allergy to be one of the important explanations for the lack of correlation existing between skin food tests and clinical sensitivity.

THE HEADACHE PROBLEM

The results of a study of approximately 5,000 individuals with headaches have been reported by Ogden[103]. This monograph was written for lay consumption and should be of value to the individual who suffers from recurring or chronic headaches. It is recognized that not all headaches are on an allergic basis, but the importance of allergy as a factor in headache is given due recognition by this author.

Vascular headaches are classified by Ouer[104] as being classic migraine, migraine variants, histaminic cephalalgia, tension headache, arteritis of the cranial vessels and of the hypertensive type. Migraine differs from histaminic cephalalgia in that the patient presents a positive family history of either headache or allergy. The attacks occur early in life, an aura is present and the attacks last many hours or days. No positive family history is given by the patient with histaminic cephalalgia. In this disorder there is no aura, the headaches are of shorter duration, and occur during the night or on awakening in the morning. Frequently daily remissions are noted between attacks with no associated nausea and vomiting. In the consideration of vascular headaches Ouer believes that there are two major points that must be made; namely, the prevention of the headache or the relief of the pain when the attack occurs. In preventing the attack of headache, elimination or reduction of the factors which may be operating to produce the headache is necessary. These factors may be trigger mechanisms and may be present in various degrees. Neurogenic, allergic, endocrine and hereditary or constitutional factors are the most common. An environmental or dietary plan must be outlined for these patients. Treatment must be directed at any one or more of the factors which will "trigger" or precipitate an attack. In treatment and relief of the pain, most patients will find the ergotamine derivatives to be of the most value. If the oral route of medication is not tolerated or is ineffective, the preparation may be given either rectally or intramuscularly. Ouer has found a new suppository, prepared from ergotamine and caffeine with algin derivative as the base, to be most helpful in extending relief to these patients.

Allergy is an important factor in the etiologic diagnosis of headaches and in some instances may be the single cause of specific types of headaches. Unger[145] states that allergic headaches fall into three groups—those associated with frank nasal allergy, the so-called allergic headaches which are primarily frontal but occasionally occipital, and vascular headaches including migraine. He defines migraine as a periodic vascular headache characterized by throbbing, severe, usually unilateral pain accompanied by nausea and photophobia, with multiple etiologic factors includ-

ing allergy. The headaches frequently may be inherited. True migraine may be reproduced by intravenous histamine with the pain appearing after cessation of the initial histamine headache, which is due to cerebral vasodilation by the histamine. The main precipitating cause of most attacks of migraine has been food sensitivity. The specific causes for the headaches are found through the use of elimination diets, feeding tests and food diaries. Skin tests rarely are beneficial. One important point brought out by this author is that any patient suffering with chronic disease will in time develop emotional tension as a result of that disease. This is true in migraine as in any other instance.

Friedman and von Stroh[55] have reviewed the value of ergotamine in patients with migraine headaches. The ergot alkaloids produce powerful reactions in the central nervous system and act as a stimulus or depressor to this system. It is thus possible that some of the psychic effects of this alkaloid may be responsible for the mood changes in patients taking large amounts of ergot. One of the most characteristic effects of the ergot alkaloids is the direct stimulation of smooth muscle in many organs. These alkaloids possess a significant adrenergic-blocking activity although the dosage used in treatment of patients with headache is hardly large enough to produce this change. Untoward side effects of ergotamine are listed as nausea and vomiting, coronary spasm, muscular cramps (chiefly in the neck and thighs) and ergotism (characterized by numbness, cyanosis and paresthesia in the extremities). This latter may lead eventually to gangrene. Fortunately ergotism rarely is found in patients who use the drug in the treatment of migraine. Though there are certain dangers associated with the use of ergotamines, this type of therapy still remains the treatment of choice in migraine. These authors have reported five cases in whom the additional danger of toxic effects of ergot has been recognized. In some individuals using ergotamine to relieve headache, the drug itself may lead to an increased frequency of these complaints. This is rather substantial evidence that the increased frequency of headaches must be related to the development of a tolerance to the drug.

MÉNIÈRE'S SYNDROME

Ménière's syndrome may be based upon an allergic background with food being the specific offender. Wittich[151] has found skin tests to be of little value in these instances. It is the opinion of most otolaryngologists that fatigue, worry, and tension play an important contributing role in producing the vascular changes which initiate this syndrome. The proper management of Ménière's syndrome is the relief of the acute symptoms. Mild sedation with a curtailment of the patient's activities is quite essential. Thorazine® in a dosage of 25 mg is a satisfactory control of vomiting. The sensation of motion sickness is readily relieved by Dramamine,® 50 mg, three times daily. This drug, too, may act as a mild satisfactory sedative. For the severe acute attack, 2.75 mg of histamine diphosphate is used. One mg of the base (representing 2.75 mg of the histamine diphosphate) in 1 cc of the concentrated solution is given in 250 cc of 5 per cent glucose solution. The rate of flow of the histamine solution should be slow, not exceeding forty drops per minute at the time of onset. If no flush or headache occurs, the rate should be accelerated slowly up to sixty drops. The prolonged flush, required in other uses of histamine, has no advantage in the relief of the severe Ménière's syndrome. The frequency and dosage of the intravenous injections depend upon the rapidity

of the disappearance of symptoms and the patient's improvement. Preventive measures may help, particularly if the symptoms of Ménière's syndrome occur early in life. Many patients with this symptom-complex notice their symptoms on awakening in the morning; Thorazine taken at this time may be of some help in aborting the subsequent attack.

In a study of fifty-five cases of Ménière's disease, six proved to have an allergic etiology. Derlacki[36] was able to give one patient complete relief by the avoidance of milk in his diet. Good response to adequate treatment has been noted in those patients with an allergic background. In the nonallergic patients, satisfactory results were obtained by this author with subcutaneous injections of histamine and the administration of potassium chloride along with low salt dietary management.

Before an accurate diagnosis of Ménière's disease can be made, it is important to exclude chronic middle ear disease, lesions of the central nervous system, vascular changes affecting the auditory nerve and toxic labyrinthitis. Holmberg[71] is very hesitant to make a diagnosis of Ménière's disease in connection with ordinary dizziness. Conservative medical therapy has proved less effective if the symptoms have existed over a long period of time. Most patients with Ménière's disease possess tension and anxiety states, and often are benefited by the use of ordinary sedatives. A low salt diet is recommended because of the increase of capillary permeability resulting in disturbed water metabolism. Fluid restriction is another suggestion that has met with some satisfactory results. The multiplicity of available preparations to relieve or abort the Ménière's symptoms is highly suggestive that no specific measures have been determined as yet.

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149. Wilhelm, R.; Nutting, H.; Devlin, H.; Jennings, E., and Brines, O.: Antihistaminics for allergic and pyrogenic transfusion reactions. J.A.M.A., 158:529, (June 18) 1955.
150. Winton, S. S., and Nora, E. D.: Immunologic aspects of penicillin reactions. Am. J. Med. 18:66 (Jan.) 1955.
151. Wittich, F. W.: Ménière's syndrome and its management. (Special Article). Quart. Rev. Allergy & Applied Immunol., 9:232 (June) 1955.
152. Wolf, A. F., and Hightower, N. C.: The clinical use of natural and synthetic endocrine products. M. Clin. North America, 39:1209 (July) 1955.

1320 Second Avenue, S.E.

In Memoriam

EDGAR O. BREAKSTONE

On November 3, 1955, a very fine gentleman and excellent doctor died in Chicago, Illinois. Dr. Edgar O. Breakstone of 11200 South Michigan Avenue, was very much interested in allergy, as well as non-medical literature and his own specialty, ophtho-otolaryngology.

Dr. Breakstone was born March 26, 1908, in Ambridge, Pennsylvania. He attended the University of Pittsburgh, from which he was graduated with a B.S. degree in pharmacy in 1930. He then went on to study medicine at the Chicago Medical School and was graduated in 1935. His internship was taken at the Cook County Hospital. Having studied ophthalmology at the University of Illinois, Dr. Breakstone became a resident in ophtho-otolaryngology at the Cook County Hospital, and taught ophthalmology at the University of Illinois from 1946 to 1950. He furthered his medical education in 1951 by taking a postgraduate course in allergy at the Cook County Hospital Graduate School.

He was a member of the Chicago Medical Society and the American Medical Association. On January 11, 1951, he was certified in otolaryngology, and served on the staff of the Chicago Eye, Ear, Nose and Throat Hospital. He had been an associate Fellow of the American College of Allergists since February 11, 1954, and was also a member of the Academy of Otolaryngology.

The officers and members of the College extend their sincere sympathy to Dr. Breakstone's wife, Alta, and to his nine-year-old son and six-year-old daughter.

C. OTTO ROSENDAHL

Dr. C. Otto Rosendahl, an Associate Fellow of the College, and Professor Emeritus of the Department of Botany at the University of Minnesota, died March 4, 1956, after a long illness. He served the College in many ways as consultant on problems relating to botany.

Dr. Rosendahl was born October 24, 1875, at Spring Grove, Minnesota. He was graduated from the University of Minnesota with a B.S. degree in 1901, and received his M.S. in 1902 at Minnesota and his Ph.D. in 1905 in Berlin, Germany. His career in the Botany Department at the University of Minnesota covers a period of forty-three years. Beginning as instructor in the department in 1901, he was made assistant professor in 1905, and full professor in 1910, a position which he held until his retirement in 1944, at which time he was made professor emeritus.

He was a member of Phi Beta Kappa and Sigma Xi, a fellow of the American Association for the Advancement of Science and the Geographical Society, a member of the Botanical Society of America, the American Society of Naturalists, the Biological Society of Washington, Torrey Botanical Club, the American Society of Taxonomists, and the Botanical Society of the Province of Brandenburg, Germany.

To his survivors and friends, the officers and members of the College extend their sincere sympathy.

Papers of Interest

Malkinson, F. D., and Ferguson, E. F.: Percutaneous absorption of hydrocortisone-4-C^{14} in two human subjects. J. Invest. Dermat., 25:281 (Nov.) 1955.

When hydrocortisone-4-C^{14} was applied to the skin, proof of its percutaneous absorption was obtained by detection of radioactivity in the urine.

Morris-Owen, R. M.: Treatment of contact dermatitis due to handling antibiotics. Brit. M. J., 1:654 (Mar. 24) 1956.

In five cases of contact dermatitis due to penicillin or streptomycin, the author was able to depress skin reactivity by injecting minute amounts of the antibiotic agent daily. After some weeks of such treatment, tolerance was acquired.

McDonald, J. H., and Heckel, N. J.: The effect of cortisone on the spermatogenic function of the human testes. J. Urol., 75:527 (March) 1956.

The spermatogenic function of adult human testes was not affected by cortisone given for periods of 23-334 days in daily doses of 75 mg.

Gable, J. J., Jr.: Jaundice associated with chlorpromazine therapy and peptic ulcer: Report of two cases. South. M. J., 48:863 (Aug.) 1955.

Margolis, L. H. et al: Nonrecurring chlorpromazine dermatitis. Arch. Dermat., 72:72 (July) 1955.

Some of the fifty-three patients developed a maculopapular dermatitis while taking chlorpromazine. Is this syndrome mediated by immune mechanisms similar to those supposedly present in thrombocytopenic purpura, other hemolytic disorders, and, perhaps, lupus erythematosus?

Mitchell, H. S., and Cooke, W. R.: Studies on the effect of morphine and related compounds on bronchial muscle. Canad. M. A. J., 73:45 (July 1) 1955.

The use of morphine appeared to be hazardous in the presence of bronchospasm or in cases of impaired choline-cholinesterase relationships. Demerol is preferred.

Epstein, S.: Hexachlorophene (G-11) in the treatment of eczematous dermatoses. Arch. Dermat., 71:692 (June) 1955.

1 to 2 per cent concentrations of hexachlorophene (G-11), added to topical medications for the treatment of eczematous dermatoses, is an effective antiseptic agent.

Eisenberg, B. C.: Contact dermatitis from selenium sulfide shampoo. Arch. Dermat., 72:71 (July) 1955.

Selenium sulfide shampoo can sensitize the skin of the neck and external ear, and produce contact dermatitis. Three such cases are described.

Davies, B. M., and Williams, D. A.: Use of corticotrophin gel and cortisone in treatment of severe and intractable asthma. Brit. M. J., 2:293 (July 30) 1955.

A good corroborative study with indications, contraindications, and doses.

Calvert, R. J., and Smith, E.: Penicillin anaphylactoid shock. Brit. M. J., 2:302 (July 30) 1955.

A short review and a case report.

Ferrara, R. J., and Pinkus, H.: Alseroxylon in the treatment of pruritic and psychogenic dermatoses. Arch. Dermat., 72:23 (July) 1955.

Rauwolfia relieved or decreased pruritus in all patients except one with urticaria.

Maspetiol, R.; Grenet, J.; Chauvet, A.; and Mlle. Desbois: Hydrocortisone in the treatment of chronic maxillary sinusitus in children. Presse méd., 64:530 (Mar. 21) 1956.

Intrasinsusal injections were beneficial to the majority of the nineteen patients studied.

Editorial: Remedies for cough. Brit. M. J., 1:340 (Feb. 11) 1956.

Relative efficacies of drugs in suppressing cough induced electrically, mechanically and clinically in cats, dogs and guinea pigs were studied. Great differences between results with methadone and other given drugs were tabulated.

Kuhns, W. J.: Types and distribution of antibodies. Am. J. Med., 20:251 (Feb.) 1956.

A review and an extensive bibliography.

Brodie, B. B.: Pathways of drug metabolism. J. Pharm. & Pharmacol., 8:1 (Jan.) 1956.

A review with thirty-eight bibliographic references to work being done.

Shilkret, H. M.: Occupational factors in asthma. New York State J. Med., 56:420 (Feb. 1) 1956.

Eagle, H., and Saz, A. K.: Antibiotics. Ann. Rev. Microbiol., 9:173, 1955.

The basis of this review is 408 references, covering biosynthesis and chemistry, mode of action, resistance, synergism and antagonism, and untoward complications.

News Items

THE AMERICAN COLLEGE OF ALLERGISTS FELLOWSHIP REPORT

The College is pleased to announce the names of those who have been promoted to Fellowship and accepted as new Fellows, Associate Fellows, and Corresponding Fellows from April, 1955, to April, 1956.

Promotions to Fellowship

Appel, William, M.D., 310 Bronson Medical Center, Kalamazoo, Michigan
Cagan, Maclyn, M.D., 33 Lincoln Park, Newark, New Jersey
Colombo, N. John, M.D., 39 Church Street, Hudson, Massachusetts
Eidinger, Samuel L., M.D., 1426 Bishop Street, Montreal, Quebec, Canada
Geraghty, Thomas P., M.D., 1045 Medical-Dental Building, Seattle, Washington
Hillman, Maurice M., M.D., 31 Howe Street, New Haven, Connecticut
MacLaren, Walter R., M.D., 136 North Madison Avenue, Pasadena, California
Manuel, Harley S., M.D., 270 South Grant Avenue, Columbus, Ohio
Miller, Ben N., M.D., 1433 Gregg Street, Columbia, South Carolina
Missal, S. C., M.D., 9119 Miles Avenue, Cleveland, Ohio
Philson, Arthur D., M.D., 421 Huguenot Street, New Rochelle, New York
Scherr, Merle S., M.D., Fitzsimmons Army Hospital, Denver, Colorado
Siegel, Sheldon, M.D., 5830 Overhill Drive, Los Angeles, California
Smith, Robert F., M.D., 665 East Market Street, Akron, Ohio
Taylor, Andrew D., M.D., Doctors Building, Charlotte, North Carolina
Wiener, Israel, M.D., 13011 West McNichols Road, Detroit, Michigan

Fellows (New Members)

Eisenberg, Ben C., M.D., 2680 Saturn Avenue, Huntington Park, California
Feingold, Ben F., M.D., 2425 Geary Boulevard, San Francisco, California
McGovern, John P., M.D., 1430 Tulane Avenue, New Orleans, Louisiana

Associate Fellows

Abrahams, Sam, M.D., 163 East Walton Place, Chicago, Illinois
Anderson, Edwin R., M.D., 514 West Third Avenue, Warren, Pennsylvania
Aronoff, Solomon, M.D., 50 Glenwood Avenue, Jersey City, New Jersey
Baxter, Edward J., M.D., 122 West Madison Street, Sandusky, Ohio
Bena, James H., M.D., 902 North Broadway, Pittsburg, Kansas
Bolker, Abraham, M.D., 2885 SW 3rd Avenue, Miami, Florida
Bressler, Edward C., M.D., 185 Lexington Avenue, Passaic, New Jersey
Brown, Elizabeth L., M.D., 39-04—48th Street, Long Island City, New York
Caplin, Irvin, M.D., 3120 North Meridian Street, Indianapolis, Indiana
Carroll, Catherine C., M.D., 5365 W. Devon Avenue, Chicago, Illinois
Cohen, Herman, M.D., 3529 Pine Tree Drive, Miami Beach, Florida
Connor, Audrey M., M.D., 3130 Wisconsin Avenue NW, Washington, D. C.
Davis, W. Grayburn, M.D., 1801 Williams, Denver, Colorado
Dean, John L., Jr., M.D., 407 East Lamar, Crockett, Texas
Don, Rita L., M.D., 616 Mills Building, El Paso, Texas
Evans, Hugh J., M.D., 215 Medical Arts Building, Tulsa, Oklahoma
Feldman, Frank H., M.D., 115 Lyons Avenue, Newark, New Jersey
Florio, Aldo, M.D., 1120 Wyatt Street, Bronx, New York
Gabelman, Charles G., Jr., M.D., 5125 East Yale Avenue, Denver, Colorado
Gershenfeld, Marvin A., M.D., 53 Jay Street, Geneva, New York
Gershenson, Wilbur, M.D., 130 West 47th Street, New York, New York
Johnson, James H., M.D., 185 North Wabash Avenue, Chicago, Illinois
Keiser, E. Lee, M.D., 256 West Douglass St., Reading, Pennsylvania
Keiter, W. Eugene, M.D., 400 Glenwood Avenue, Kinston, North Carolina
Lovell, William F., M.D., 207 Hawthorne Lane, Charlotte, North Carolina
Miller, Ervin R., Sr., M.D., 416 North Manus Drive, Dallas, Texas
Montag, Leonard, M.D., 2200 Santa Monica Boulevard, Santa Monica, California
Morton, Jean C., M.D., 9311 Milroy Place, Bethesda, Maryland
Perez-Toledo, A., M.D., 1812 Ponce de Leon Avenue, Santurce, Puerto Rico

Sallee, Jack C., M.D., Medical Arts Building, Wilmington, Delaware
Shivers, Olin, M.D., 33 Ponce de Leon Avenue NE, Atlanta, Georgia
Siegel, Clarence, M.D., 1163 Lowry Medical Arts Building, St. Paul, Minnesota
Smith, Douglas L., M.D., 59 West Central Avenue, Delaware, Ohio
Stadtner, David A., M.D., 425 North California Street, Stockton, California
Sullivan, Nicholas P., M.D., 304 Medical Center, Eugene, Oregon
Szanton, Victor L., M.D., 259 Main Street, Ansonia, Connecticut
Weiner, Harry, M.D., 2136 Hillsboro Avenue, Los Angeles, California
Wilson, William H., M.D., 1414 East Fremont, Las Vegas, Nevada
Zucker, Albert, M.D., 315 East 167th Street, Bronx, New York
Zuckerman, Sidney, M.D., 109-23—71st Road, Forest Hills, New York

Corresponding Fellows

Alemany-Vall, Roman, M.D., Av. del Generalisimo Franco, 331, 1°, 2°, Barcelona, Spain
Kimura, Yoshitami, M.D., 59 Komagone-Sendagi-cho, Bunkyo-ku, Tokyo, Japan
Liebeskind, Aleksander, M.D., 107 Arlosoroff Street, Haifa, Israel
Nakamura, Keizo, M.D., 59 Komagone-Sendagi-cho, Bunkyo-ku, Tokyo, Japan

EARLIER PUBLICATION DATE FOR 1957 CONVENTION PROGRAM

Due to the fact that the Graduate Instructional Course and Thirteenth Annual Meeting of the College occurs earlier next year, March 17-22, 1957, the program will appear in the November-December, 1956 issue of the ANNALS OF ALLERGY, rather than in the January-February, 1957, number. Those Fellows who wish to present papers at the general session or who wish to be instructors at the postgraduate course should therefore communicate with the respective chairmen before October 1, 1956.

POSTGRADUATE COURSE IN PEDIATRIC ALLERGY

The New York Medical College Flower and Fifth Avenue Hospitals, Division of Graduate Studies, Department of Graduate Pediatrics, announces a postgraduate course in pediatric allergy, under the direction of Dr. Bret Ratner, Professor of Clinical Pediatrics and Associate Professor of Immunology, to be held on Wednesdays from 9:00 a.m. to 4:00 p.m., November 7, 1956 through May 27, 1957, a total of thirty sessions. The course consists of lecture-seminars, laboratory and clinical procedures, clinic work, ward rounds and animal experimentation covering the basic principles of diagnosis and treatment of allergy in children, and applied immunology A fee of $300 will be charged, and all applicants must be certified in pediatrics or have the requirements for certification. Further information may be obtained from the Office of the Dean, New York Medical College, Fifth Avenue at 106th Street, New York 29, New York. A research felowship in pediatric allergy is available, for which immediate application should be made.

NEWS OF MEMBERS

Dr. Ellis April has recently been appointed as a consultant (allergy) to the American Medical Association's Council on Pharmacy and Chemistry.

BOOK REVIEWS

ÉLÉMENTS D'IMMUNOLOGIE GÉNÉRALE. P. Gastinel, R. Fasquelle, and P. Barbier. 335 pages with index. Paris, France: Masson & Co., 1955. 2,000 Francs.

Few American physicians would wish to review their immunology from a French text, but Drs. Gastinel, Fasquelle and Barbier, all of the Faculty of Medicine in Paris, have done a remarkable piece of work in preparing a book suitable both for students of bacteriology and immunology and research workers in both fields. Of chief interest to allergists is a series of studies dedicated to types of immunologic reactions seen in anaphylaxis, allergy and active or passive immunity.

The bibliography lists the number of studies not generally included in papers published in this country. The authors show themselves familiar with the world literature in this field. The language is lucid, and the twenty-six figures well drawn and clear.—*E.A.B.*

THE ROLE OF ALGAE AND PLANKTON IN MEDICINE. Morton Schwimmer, M.D., Clinical Assistant in Medicine, and David Schwimmer, M.D., F.A.C.P., Assistant Professor of Medicine, The New York Medical College, Metropolitan Medical Center, New York, New York. 85 pages with index. New York & London: Grune & Stratton, 1955. Price, $3.75.

This monograph on the role of algae and plankton in medicine is the first medical survey of the field. The macroscopic algae (seaweeds) have been used nutritionally and medically since prehistoric times. The list of conditions for which they are in use at present includes goiter, dropsy, hepatic, digestive and renal disorders, constipation, and obesity, among others. The alginates are, at present, used as wound dressings, molds for applying skin grafts, hemostatics in brain and thoracic surgery, as decontaminants in the treatment of mustard gas poisoning and burns, as swabs in the bacteriologic examination of eating utensils, and as a replacement for tragacanth and other gums in the manufacture of lubricating jellies. More than 50 per cent of the ice cream made in this country is stabilized with algin.

Of chief interest to allergists are the number of states of intoxication with microalgae associated with respiratory symptoms. Fitch tested guinea pigs with *Microcystis* and *Anabaena* which had killed cattle in Minnesota. The characteristic symptoms in guinea pigs included restlessness, incontinence, deep breathing, sneezing, coughing, salivation, lacrimation, weakness in the hind quarters, clonic spasms and death. Rabbits presented the same picture and, in addition, opisthotonus.

Mason and Wheeler injected *Microcystis* extract into mice, rats, guinea pigs and cats. Following a latent period there appeared pallor, hypotension, tachycardia, hypothermia, hyperglycemia, respiratory difficulty and death. In Smit's experiments with *Microcystis* fed to rabbits, there was restlessness, dyspnea, progressive paralysis, coma and death within four hours.

In humans, Heise has, on two occasions, described *Oscillatoraceae* as directly causing itching, conjunctivitis, nasal stenosis and bronchospasm in a fifty-seven-year-old male, and again, swollen eyelids, nasal stenosis and an urticarial reaction in a thirty-nine-year-old female. Other allergic manifestations include the urticarial-papular, "seabathers eruption" described by Sams and also by Ayres.

Indirectly, algae ingested by mussels, eels and fish cause poisoning associated with death due to respiratory failure. *Scombroid* poisoning results from the eating of various topical types of tuna, and manifests itself as a histamine-like headache with

flushing of the face, conjunctivitis, giant hives, erythema and a gastric upset with recovery in eight to twelve hours.

The author states that "the number of disease syndromes attributable to algae comes rather as a surprise and raises some interesting questions. The most obvious afflictions are the allergic dermatitides resulting from bathing in water contaminated with algae. Also understandable are the respiratory irritations from water-borne or inhaled algae; in fact, many cases of allergic rhinitis (and its corollary, chronic sinusitis) in coastal areas might be traceable to algae instead of being blamed on damp climate or that handy favorite of allergists, dust."

This little book makes suggestive and interesting reading in a field little known to the general reader.—*E.A.B.*

APPOINTMENT ANNOUNCED

Dr. Harry L. Alexander, Professor Emeritus of the School of Medicine, Washington University, St. Louis, has been appointed to serve on the National Advisory Allergy and Infectious Diseases Council. In this capacity he will assist in giving advice and recommendations to the Surgeon General of the U. S. Public Health Service regarding grant activities of the National Institute of Allergy and Infectious Diseases, Bethesda, Maryland.